

**Development of Drugs to Treat Multi-Drug Resistant
Tuberculosis (MDR-TB)**

AIDAC Advisory Committee Meeting

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Glossary of Abbreviations and Acronyms

AFB	<i>Acid-fast bacilli</i>
AIDS	<i>Acquired immunodeficiency syndrome</i>
Am	<i>Amikacin</i>
Amx/Clv	<i>Amoxicillin/clavulanate</i>
ART	<i>Antiretroviral therapy</i>
ARV	<i>Antiretroviral drug</i>
CDC	<i>Centers for Disease Control and Prevention</i>
Cfz	<i>Clofazamine</i>
Clr	<i>Clarithromycin</i>
Cm	<i>Capreomycin</i>
Cs	<i>Cycloserine</i>
CXR	<i>Chest X-ray</i>
DDI	<i>Drug-drug interaction</i>
DR-TB	<i>Drug-resistant Tuberculosis</i>
DOT	<i>Directly observed treatment</i>
DST	<i>Drug susceptibility testing</i>
EMB or E	<i>Ethambutol</i>
Eto	<i>Ethionamide</i>
EPTB	<i>Extrapulmonary tuberculosis</i>
FQ	<i>Fluoroquinolone</i>
GLC	<i>Green Light Committee</i>
HAART	<i>Highly active antiretroviral therapy</i>
HIV	<i>Human immunodeficiency virus</i>
Imp/Cln	<i>Imipenem/cilastatin</i>
INH or H	<i>Isoniazid</i>
Lfx	<i>Levofloxacin</i>
Lzd	<i>Linezolid</i>
Km	<i>Kanamycin</i>
MDR-TB	<i>Multidrug-resistant TB (resistance to at least rifampicin and isoniazid)</i>
Mfx	<i>Moxifloxacin</i>
MRC	<i>Medical Research Council</i>
NNRTI	<i>Non-nucleoside reverse transcriptase inhibitor</i>
NRTI	<i>Nucleoside reverse transcriptase inhibitor</i>
NTP	<i>National tuberculosis programs</i>
Ofx	<i>Ofloxacin</i>
PAS	<i>p-aminosalicylic acid</i>
PI	<i>Protease inhibitor</i>
PTB	<i>Pulmonary tuberculosis</i>
Pto	<i>Protionamide</i>
PZA or Z	<i>Pyrazinamide</i>
Rfb	<i>Rifabutin</i>
RIF or R	<i>Rifampicin</i>
SM or S	<i>Streptomycin</i>

T or Thz	<i>Thioacetazone</i>
TB	<i>Tuberculosis</i>
TB/HIV	<i>HIV-related TB</i>
Trd	<i>Terizidone</i>
USPHS	<i>United States Public Health Service</i>
VIO	<i>Viomycin</i>
WHO	<i>World Health Organization</i>
XDR-TB	<i>Extensively-resistant tuberculosis (TB that are MDR strains that are also resistant to a fluoroquinolone and, at least, one second line injectable agent (amikacin, kanamycin and/or capreomycin))</i>

1. Overview

In 2007, the World Health Organization (WHO) estimated 10.4 million cases of tuberculosis (9.27 first episodes, 1.16 subsequent episodes in patients who had previously experienced at least one previous episode of tuberculosis, TB) worldwide. An estimated 4.9% or 511,000 of these cases met the definition of multidrug-resistant tuberculosis (MDR-TB, see below), where 289,000 were new cases (3.1% of all new cases) and 221,000 were among cases that had been previously treated for TB (19% of all previously treated cases).¹

According to 2008 data from the CDC, a total of 12,898 incident TB cases were reported in the United States. Although overall TB rates have declined in the United States, drug-resistant strains of the disease are increasing, particularly among the foreign-born population residing in the U.S.

MDR-TB is defined as TB caused by organisms that are resistant to isoniazid (INH) and rifampin (RIF). MDR-TB is the focus of this document, although other degrees of resistance to anti-TB drugs, ranging from single drug (monoresistance) to extensively drug-resistant (XDR-TB) also exist.

MDR-TB poses a significant global and public health issue. According to a recent meta-analysis of MDR-TB studies that used second-line drugs in individualized or standardized protocols, the overall treatment success defined as the proportion of patients who were cured or completed treatment, ranged from 36% to 79%.² This is in contrast to the greater than 95% treatment success rate has been consistently obtained with modern combination drug regimens for the treatment of drug-susceptible TB since the late 1970s.³ Related to this low efficacy rate is a considerable mortality rate, particularly in the HIV co-infected population, observed in those infected with MDR-TB strains compared to susceptible ones. The treatment of MDR-TB requires the use of many drugs with significant adverse effects for a minimum of 18 to 24 months. While non-compliance with medications and the morbidity associated with drug-interactions and drug adverse events are major concerns in the management of this disease, these issues are only magnified in the co-infected HIV population on antiretroviral therapy. Lastly, the low efficacy rate in MDR-TB means that many patients treated will go on to develop chronic, highly resistant forms of TB that can be transmitted to others. Therefore, there is an increasing need for clinical trials that will identify safe and effective regimens for the treatment of this disease.

¹ World Health Organization. Global Tuberculosis Control: epidemiology, strategy, financing. WHO Report 2009. WHO/HTM/TB/2009.411:
http://www.who.int/tb/publications/global_report/2009/pdf/full_report.pdf

² Orenstein EW, Basu S, Shah NS, Andrews JR, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. *Lancet Infect Dis* 2009;9:153-61.

³ Sacks LV, Behrman RE. Developing new drugs for the treatment of drug-resistant tuberculosis: a regulatory perspective. *Tuberculosis (Edinb)*. 2008; 88Suppl 1:S93-100.

In contrast to drug-susceptible TB, treatment of drug-resistant TB (DR-TB) is not based upon randomized clinical trials, but cohort and case-series analyses and expert opinion. Treatment guidelines for DR-TB are published by the WHO (Guidelines for the Programmatic Management of Drug-resistant Tuberculosis, Emergency Update 2008) for use globally.⁴ In addition, the American Thoracic Society (ATS), CDC, and more recently the Infectious Disease Society of America (IDSA) have collaborated to develop joint guidelines (Guidelines for the Treatment of Tuberculosis) for the diagnosis, treatment, prevention, and control of tuberculosis, including DR-TB, in the United States.⁵

Due to the long duration of treatment of 18 to 24 months, as well as a period of follow-up after treatment in order to assess relapse, clinical trials of investigational drugs for MDR-TB are costly and fraught with such practical issues as high rates of loss to follow-up with increasing duration of the trial. Since MDR-TB is considered a serious and life-threatening disease, it qualifies for study under Accelerated Approval (Subpart H) regulations (21 CFR 314.500). Approval by this mechanism requires drugs to show a therapeutic benefit over existing treatment and identification of a surrogate endpoint likely to predict clinical benefit or a clinical endpoint other than survival.

Thus as a first step for MDR-TB trials to qualify for Subpart H, a clinically meaningful early endpoint must be identified where experience to date has demonstrated its ability to reasonably predict mortality/relapse of disease. The following section provides further detail on study design considerations for MDR-TB trials and the objectives for holding this Advisory Committee meeting on drug development for MDR-TB.

2. Introduction to Advisory Committee Meeting on MDR-TB

Although treatment cure rates in patients with susceptible tuberculosis are considered high, comparable success rates are not seen in the treatment of drug-resistant tuberculosis, including multi-drug resistant tuberculosis. Regimens for the treatment of MDR-TB tend to yield low efficacy rates and patients need to be on multiple drugs, receive treatment for many months to years, and may develop toxicity. Therefore, new drugs to treat MDR-TB are needed. The committee is being asked to discuss issues related to the development of drugs for the treatment of TB, specifically MDR-TB. Primary topics for discussion include specific issues related to study design, such as endpoints and duration of follow-up to assess outcome, and evaluation of drug safety.

The meeting will focus on issues related to MDR-TB, and will not deal in depth with susceptible TB, latent TB, or extensively-resistant TB. However, because the literature on susceptible tuberculosis is both more extensive and includes numerous comparative

⁴ World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency Update 2008. Document no. WHO/HTM/TB/2006.402. Geneva: WHO, 2008: http://www.who.int/tb/publications/global_report/2008/en/

⁵ American Thoracic Society, CDC, and Infectious Diseases Society of America. Treatment of Tuberculosis. MMWR. June 20, 2003;52(RR11);1-77.

trials, information from publications on susceptible TB trials is provided for background and for perspective to facilitate discussion of the issues relative to MDR-TB.

Treatment for MDR-TB generally lasts between 18 and 24 months. To assess the effect of investigational drugs on the clinical outcome of interest, namely mortality or relapse of disease, a period of observation following the treatment period is required. At this time it is unclear exactly how long and how often subjects should be followed. It is understood that the longer the follow-up period, the larger the number of subjects will be who have missing data and the more uninterpretable the study results will be.

Since MDR-TB is considered a serious and life-threatening disease, drugs to treat MDR-TB qualify for approval under Accelerated Approval (Subpart H) regulations (21 CFR 314.500). This approach is applicable for drugs that show a meaningful therapeutic benefit over existing treatments. Approval may be granted on the basis of adequate and well-controlled clinical trials showing the drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or an effect on a clinical endpoint other than survival. As part of the accelerated approval regulations, sponsors are required to verify and describe a drug's clinical benefit, for example, by completing the long-term follow-up to evaluate mortality or relapse. For a surrogate endpoint, this means evaluating the surrogate endpoint's benefit in relation to clinical benefit, and for a clinical endpoint evaluating the relationship to ultimate outcome.

For MDR-TB, there are various endpoints that can be used to describe early outcome, most of which are microbiologic endpoints such as: early bactericidal activity, sputum smear, sputum culture conversion, serial sputum colony counts, and time to sputum culture conversion. This document discusses the utility and limitations of each of these endpoints (see Section 4.1 "Early Endpoints").

Any early microbiologic endpoint that is selected for use under Subpart H regulations must show that it is likely to predict clinical benefit or otherwise be clinically meaningful. Therefore, it would be expected that clinical trials collect data on the early endpoint (e.g., microbiological) along with clinical, and radiological data, to evaluate efficacy. In addition, it should be noted that clinical symptom resolution should generally correlate with microbiologic response. Additional discussion is needed on whether any of these early endpoints is sufficient to allow development of a TB drug under Subpart H.

A second topic of discussion is the time point at which these endpoint(s) should be assessed. In tuberculosis trials, mostly derived from studies of susceptible tuberculosis, an early time point(s) is often evaluated to determine when mycobacteria are no longer present in the sputum, and a later time point(s) is evaluated to determine whether patients relapse. In older publications, but not consistently found in more recent publications, data on the clinical response to treatment (e.g., resolution of fever, cough, weight gain) and radiological response (e.g., changes in radiological findings) were often collected. In order to address this topic of time points, published data, including data obtained from the studies of Priftin® (rifapentine) in susceptible tuberculosis, were reviewed to describe the correlation between sputum culture conversion and relapse. As much of the data discussed pertains to drug-susceptible disease, the applicability to MDR-TB is unclear.

Under Subpart H, clinical trials must not only evaluate an early endpoint, but must also obtain long-term data to assess whether the clinical benefit seen with the early endpoint adequately predicts the long-term clinical outcome. Usually, these long-term studies are a continuation of studies already underway, although additional trials to evaluate clinical benefit may also be warranted. If these long-term results confirm the safety and efficacy of the drug(s) approved under Subpart H, then the drug is considered to have fulfilled the requirements for traditional approval. If the clinical study fails to verify the early clinical benefit or there are safety issues, FDA regulations state that FDA may withdraw approval of the drug (21 CFR 314.530).

Significant mortality is observed in patients with MDR-TB, especially in patients co-infected with HIV. However, a reduction in mortality attributable to a new drug may be difficult to demonstrate in a clinical trial. Additional discussion will be invited on clinical trial designs that may foster assessment of such an endpoint as the long-term clinical endpoint of interest.

In trials of drug-susceptible TB, relapse at 24 months following the end of treatment is generally used as the long-term endpoint of interest in evaluating clinical benefit. The use of this endpoint in drug-susceptible disease is supported by literature data which suggest that most relapses occur by this time. In MDR-TB the literature on relapse is limited by the fact that treatment regimens are only about 50-60% effective, thereby reducing the number of patients who can be assessed for relapse, since sputum clearance is a prerequisite. Discussion at this meeting should also focus on whether relapse is the appropriate long-term clinical outcome of interest in MDR-TB and the appropriate timing of assessment of relapse following the end of therapy. In addition, given the long duration of treatment and therefore studies to evaluate outcome of treatment, the level of evidence needed regarding relapse (or other endpoint) to support fulfilling the requirements under Subpart H to verify and describe the ultimate outcome of treatment (e.g., traditional approval) should be considered.

Patients with HIV co-infection represent a subpopulation of MDR-TB patients that requires special consideration. In general, the recommended treatment for MDR-TB is the same for HIV-positive as for HIV-negative patients; however, treatment is more difficult and deaths are more frequent. Use of ART in HIV-positive patients with drug-susceptible or drug-resistant TB can be complicated by drug-drug interactions and adverse events that may lead to loss of efficacy or interruption of both TB and/or HIV therapy. Consideration should be given to factors that facilitate or limit the inclusion of HIV-positive patients in trials for initial approval of drugs for MDR-TB and whether the early endpoint(s) and timing of those endpoints, as discussed above, apply to the HIV-positive population. In addition, the timing of an assessment of long-term clinical outcome may or may not be the same in trials of HIV-positive patients and any differences should be noted.

An extensive literature review was performed to obtain articles on MDR-TB which address endpoints, timing, and correlation with relapse, as discussed above. The

complete data tables can be found in **Appendix A (MDR-TB in HIV-negative patients), Appendix B (MDR-TB in HIV-positive patients), Appendix C (complete bibliography of articles reviewed)** and a discussion of the findings can be found in Section 4.2.1 “Summary of Published Data in MDR-TB”.

Finally, in addition to issues related to efficacy, clinical trials should also provide data on the safety of an investigational drug (including drugs approved under Subpart H). The evaluation of the safety profile of an investigational drug for treating MDR-TB can be challenging because it is administered along with other antimycobacterial drugs and other concomitant medications (e.g., antiretroviral therapy for HIV) in patients who often have co-morbid conditions. Therefore, it is important that there is sufficient safety information collected using the investigational drug as part of the anticipated clinical regimen, including information at the intended dose and duration of treatment. A discussion of safety should focus on the factors that influence the adequacy of the safety data used to support a drug application for MDR-TB, including the minimum size of a safety database for drugs to treat MDR-TB approved under both accelerated and traditional approval mechanisms.

This document is organized into a background section on the disease epidemiology and emergence of drug resistance, discussion on early endpoints and their relation to relapse, analysis of the MDR-TB literature, lessons learned from drug-susceptible disease (i.e., Prifitin) and drug approvals for antiretrovirals used in treating HIV, treatment guidelines and recommendations discussing currently available standard of care regimens and how to use them, and finishes with a general overview of clinical trial considerations.

3. Background

Tuberculosis is a significant threat to the health of populations worldwide. In 1993, the WHO declared it a ‘global emergency.’⁶ MDR-TB is an emerging threat, especially in developing countries.

MDR-TB is generally defined as tuberculosis that is caused by mycobacteria that are resistant to isoniazid (INH) and rifampin (RIF), two first-line drugs in TB treatment regimens. This document focuses primarily on issues relevant to MDR-TB, however background information on drug-susceptible tuberculosis is also included to provide perspective and to frame the issues for further discussion.

Other varying degrees of resistance exist, however, from resistance to a single agent (mono-resistance) to extensively resistant (XDR-TB). The WHO MDR-TB Treatment Guidelines define these other types of resistance as follows:⁷

⁶ <http://www.nytimes.com/1993/04/24/world/un-agency-says-rise-in-tb-is-global-crisis.html>

⁷ World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency Update 2008. Document no. WHO/HTM/TB/2006.402. Geneva: WHO, 2008: http://www.who.int/tb/publications/global_report/2008/en/

Mono-resistance: Resistance *in vitro* to one first-line anti-TB drug, namely isoniazid (INH), rifampin (RIF), ethambutol (EMB), pyrazinamide (PZA), or streptomycin (SM). (Also referred to as Drug-Susceptible Tuberculosis.)

Poly-resistance: Resistance *in vitro* to more than one first-line anti-TB drug, other than both INH and RIF.

XDR-TB: Extensively-drug resistant tuberculosis is MDR-TB plus resistance to any of the fluoroquinolones and to at least one of the three injectable second-line drugs (amikacin, capreomycin, or kanamycin).

Primary MDR-TB is tuberculosis resistant to INH and RIF in persons without any history of anti-TB drug intake (primary drug resistance) and is due to the transmission of infection of the resistant tuberculosis strains from individuals who harbor resistant strains of *M. tuberculosis*.

Secondary MDR-TB is tuberculosis resistant to INH and RIF in individuals who have or are receiving anti-TB therapy and develop resistance to INH and RIF during the treatment regimen. This can occur as a result of inadequate (insufficient dosage or duration), inappropriate first-line drug therapy, or from noncompliance.

3.1. Biologic Mechanisms of Resistance

The primary goals of anti-TB chemotherapy are to kill tubercle bacilli rapidly, prevent the emergence of drug resistance, and eliminate persistent bacilli from the host's tissues to prevent relapse. It is theorized that there are three separate subpopulations of *M. tuberculosis* within the host. These populations are defined by their growth characteristics and the milieu in which they are located.⁸ The largest of the subpopulations consists of rapidly growing extracellular bacilli that reside mainly in cavities.

Tubercle bacilli possess spontaneous and predictable rates of chromosomally borne mutations that confer resistance to antimicrobial agents.⁹ However, the frequency of these single mutations is sufficiently low that with appropriate combination chemotherapy that is reliably ingested, clinically significant resistance will not develop. Mutations are not linked and therefore resistance to a drug is generally not associated with resistance to an unrelated drug. When drug resistance emerges, it usually represents the survival of random preexisting mutations rather than a change caused by exposure to the medication. Mutations causing resistance to INH or RIF occur in roughly 1 in 10^8 to 10^9 replications of bacteria. The likelihood of spontaneous mutations causing resistance to both INH and RIF is the product of these probabilities, or 1 in 10^{16} . Because patients with even extensive TB harbor far fewer mycobacteria than this, the development of spontaneous, dual resistance is highly statistically improbable.

⁸ Mitchison DA. Mechanisms of the action of drugs in short-course chemotherapy. Bull Int Union Tuberc 1985;60:36-40.

⁹ Iseman M. Treatment of multidrug-resistant tuberculosis. NEJM 1993;329(11):784-91.

Most commonly the development of acquired drug resistance occurs when there is a large bacillary population, such as in pulmonary cavities, when an inadequate drug regimen is prescribed (inappropriate or insufficient number of drugs, insufficient dosage) or when an adequate regimen is not taken by the patient (noncompliance or poor drug absorption).

3.2.Epidemiology of MDR-TB

3.2.1. Global Epidemiology

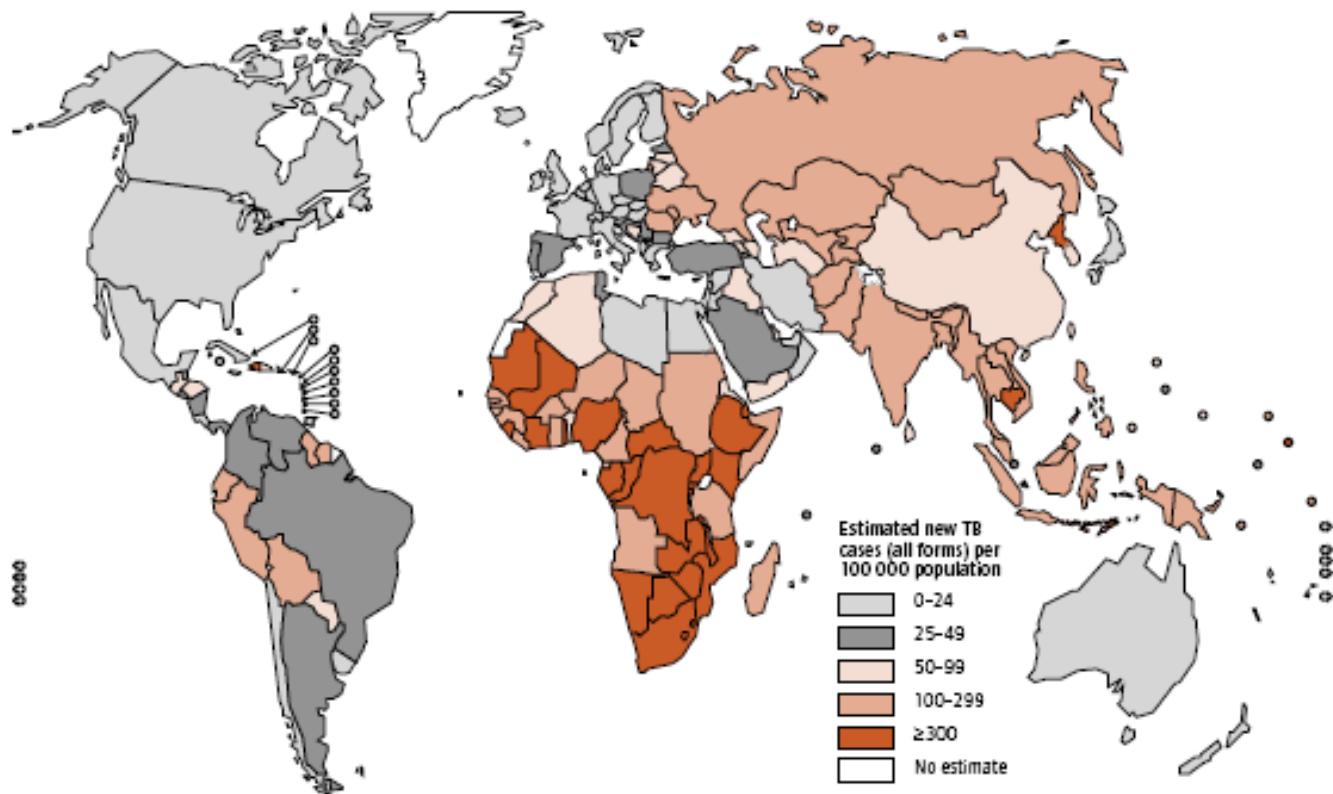
Drug-susceptible tuberculosis

There were an estimated 9.27 million incident (initial) cases of tuberculosis (TB) globally in 2007, and an additional 1.16 million subsequent episodes of TB, defined as cases occurring in patients who had already experienced at least one previous episode of TB in the past and who had received at least one month of anti-TB treatment (overall 10.4 million).¹⁰

Asia (the South-East Asia and Western Pacific regions) accounts for 55% of global cases and the African Region for 31%; the other three regions (the Americas, European and Eastern Mediterranean regions) account for small fractions of global cases. The magnitude of the TB burden within countries can also be expressed as the number of incident cases per 100 000 population (see figure below).

Of the 9.27 million incident TB cases, an estimated 1.37 million (15%) patients were HIV-positive; 79% of these HIV-positive patients were in the African Region and 11% were in the South-East Asia Region.

¹⁰ World Health Organization. Global Tuberculosis Control: epidemiology, strategy, financing. WHO Report 2009. WHO/HTM/TB/2009.411:
http://www.who.int/tb/publications/global_report/2009/pdf/full_report.pdf



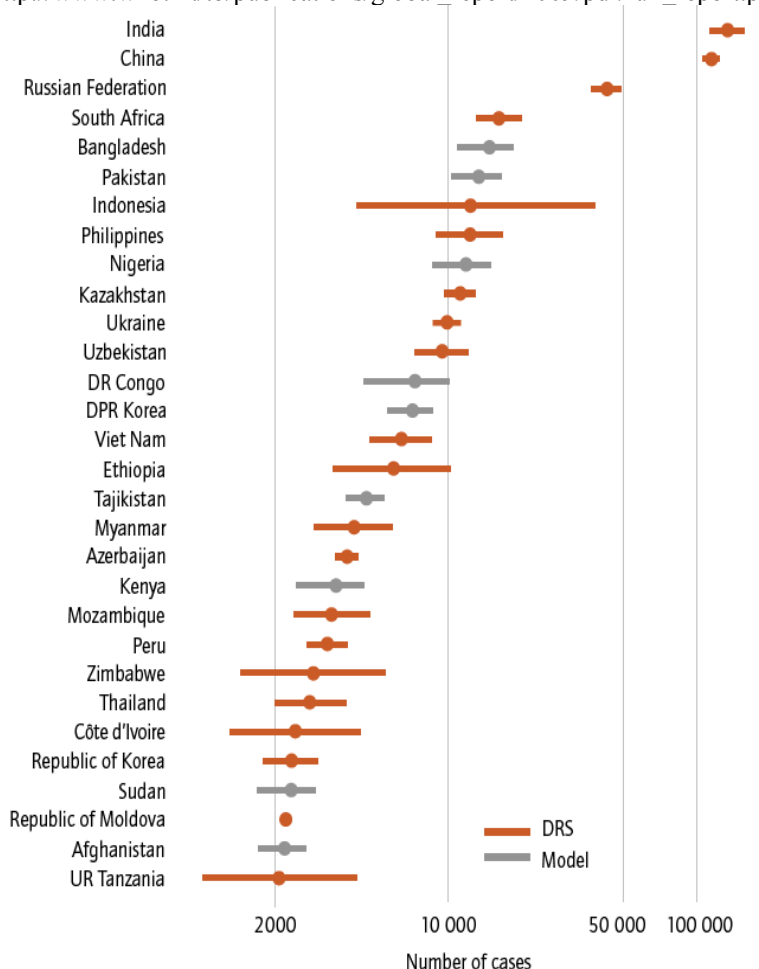
Multidrug-resistant TB (MDR-TB)

Among the 10.4 million episodes of TB (initial and subsequent), an estimated 4.9% or 511,000 were caused by MDR-TB. Of these, 289,000 were primary MDR-TB representing 3.1% of all new cases, and 221,000 were secondary MDR-TB representing 19% of all previously treated cases.

The countries with the largest number of cases of MDR-TB are shown below.

Countries with the highest numbers of estimated MDR-TB cases, 2007. Horizontal lines represent 95% confidence intervals. The source of estimates is drug resistance surveillance or surveys (, in red) or modeling (in grey)

http://www.who.int/tb/publications/global_report/2009/pdf/full_report.pdf



The WHO/IUATLD Global Project on Antituberculosis Drug Resistance Surveillance gathers data on drug resistance using a standard methodology in order to determine the global magnitude of resistance to four first-line anti-TB drugs: isoniazid, rifampicin, ethambutol and streptomycin. Based on available information from Global Project (2002-2007), data available from 116 countries and settings were weighted by the population in areas surveyed, representing 2,509,545 cases of TB. The global population weighted proportion of MDR-TB was: 2.9% (95% CI, 2.2, 3.6) among newly diagnosed TB cases; 15.3% (95% CI, 9.6, 21.1) among previously treated TB cases; 5.3% (95% CI, 3.9, 6.6) among all TB cases.¹¹

Based on drug resistance information from the 116 countries and settings reporting to this project, as well as nine other epidemiological factors, it is estimated that 489,139 (95%

¹¹ World Health Organization. Global Tuberculosis Control: epidemiology, strategy, financing. WHO Report 2009. WHO/HTM/TB/2009.411: http://www.who.int/tb/publications/global_report/2009/pdf/full_report.pdf

CI, 455,093; 614,215) cases of MDR-TB emerged in 2006. China and India carry approximately 50% of the global burden of MDR-TB and the Russian Federation accounts for a further 7%. In this report, there were greater proportions of MDR-TB among new cases than found in previous reports, ranging up to 16% MDR-TB among new cases in Donetsk, Ukraine, 19.4% in the Republic of Moldova and 22.3% in Baku, Azerbaijan. Trends in MDR-TB among new cases in the Baltic countries appear to have stabilized, but there were significant increases reported from the two regions of the Russian Federation that reported data.¹²

3.2.2. United States Epidemiology

Drug-susceptible TB

According to the CDC, in 2008 a total of 12,898 incident TB cases were reported in the United States. Foreign-born persons and racial/ethnic minorities bear a disproportionate burden of the disease, with a TB rate 10 times higher than in U.S.-born persons.

Multidrug-resistant TB (MDR-TB)

A total of 125 cases of MDR-TB were reported in 2007, the most recent year for which complete drug-susceptibility data were available. Drug-susceptibility test results for isoniazid and rifampin were reported for 97.8% (10,190 of 10,421) of culture-confirmed TB cases in 2007. The percentage of TB cases that were MDR-TB was 1.2% (125 of 10,190) among culture-positive cases with susceptibility testing performed, approximately 1% among persons without a previous history of TB, and 3.6% among persons with a previous history of TB. Foreign-born persons accounted for 81.6% of MDR-TB cases (5.2% among those with a previous history of TB and 1.5% among those without a previous history).¹³

3.3. History of Development of TB Drugs and Emergence of Drug Resistance

Early experience in clinical trials demonstrated that multiple agents are necessary to prevent the emergence of a drug-resistant population as a consequence of the selection pressure from administration of a single agent.

The discovery and use of agents with activity against *M. tuberculosis*, and the subsequent emergence of resistance to these agents, was discussed in a review article describing TB studies carried out by the British Medical Research Council's TB units and their

¹² World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency Update 2008. Document no. WHO/HTM/TB/2006.402. Geneva: WHO, 2008: http://www.who.int/tb/publications/global_report/2008/en/

¹³ Centers for Disease Control and Prevention. Trends in Tuberculosis – United States, 2008. MMWR 2009;58(10);249-253

collaborators throughout the world between 1946 and 1986.¹⁴ The following summary provides a timeline of these events.

- Streptomycin (SM) first became available in 1946 and the emergence of resistance to the drug when used alone in was documented starting in 1948.
- Also in 1948, studies using PAS in combination with SM showed that these two drugs used together induced far fewer SM-resistant strains than SM used alone.
- Isoniazid (INH) was introduced in 1952 and early trials showed resistant emerged rapidly to INH alone but resistance was almost completely suppressed by combining SM with INH.
- While the studies on INH alone and in combination were progressing, a series of papers was published between 1952 and 1955 on methods for measuring drug resistance.
- The focus of treatment during the early 1950s was preventing the emergence of drug resistance. At the same time, it was found necessary to prolong the treatment period substantially to prevent subsequent relapse.
- The first national sampling survey of primary drug resistance was carried out in Britain during 1955–1956. The prevalence of resistance was assessed by the proportion of previously untreated patients whose cultures were resistant to INH. Resistance was found to SM in 2.5%, to PAS in 2.6% and to INH in 1.3% of the sample of 974 cultures. Resistance to two or three drugs was rare.
- Over the next two decades further surveys of primary resistance were conducted in Britain, Hong Kong, Kenya and Tanzania. Resistance to INH was infrequent in the initial 1955-56 survey in Britain, and remained low in subsequent surveys at 2% or less (1963, 1978-79, 1983, and 1988). The prevalence of initial INH resistance was higher, at 10% in Kenya (1964-74) and 6% in Tanzania in 1969-70, rising to 10% in 1978-80. Hong Kong reported 14% resistance in 1962.
- Findings from the initial British drug resistance survey led to the use of a third drug at the start of treatment, since treatment of patients whose strains had primary resistance to a single drug who were treated with a two-drug regimen had outcome rates similar to monotherapy. Subsequent studies in the early 1960s showed that using three drugs in the initial phase of treatment, not only improved outcomes in patients with existing resistance, but that a three-drug combination was more effective than two-drug combinations in preventing the emergence of resistance. As a result, standard regimens of SM, PAS, INH followed by PAS and INH were used increasing throughout the world.

¹⁴ Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council Tuberculosis Units, 1946-1986, with relevant subsequent publications. *Int J Tuberc Lung Dis* 1999;3(1):S231-79.

- In the early 1970s, the first short-course regimens were born when it was demonstrated that treatment could be shortened to 6 months by the inclusion of RIF and PZA in the regimen. Patients with initial resistance to INH or SM fared almost as well as those with initially sensitive organisms, provided that RIF was given for 6 months. However, failure or relapse was common if there was initial RIF resistance, even when not accompanied by resistance to INH.

Turning to the U.S., national survey data revealed that primary resistance to INH in the period 1961-68 was 1.8%, rising to 5.3% in 1982-86, and increasing further to 8.2% in 1991.¹⁵

RIF was not available approved in the U.S. until 1971. Resistance to this agent was found in 0.6% of strains from previously untreated patients and 3% of strains from previously treated patients between 1982-86.¹⁶ Resistance to both RIF alone and to both INH and RIF increased to 3.5% in 1991.¹⁷

According to the CDC:¹⁸

- A TB epidemic occurred in the United States between 1985 and 1992 after approximately 30 years of declining trends. With implementation of elements of the 1992 National Action Plan to Combat Multidrug-Resistant Tuberculosis, reported MDR-TB cases declined rapidly between 1993 and 1999 and correlated with the overall decline in TB cases in the U.S.
- Increased use of second-line drugs beginning in the 1980s resulted in MDR-TB strains with extensive resistance to both first- and second-line drugs. Thus, XDR-TB cases being reported in the 1990s likely represented the legacy of the 1985-1992 TB epidemic and increased use of these treatments to combat the spike in MDR-TB cases.
- Characteristics of MDR TB and XDR-TB cases changed during 2000-2006 in parallel with the changing epidemiology of TB, in general. These changes included an overall decrease in the number of cases, a decrease in the proportion of cases in HIV-positive persons, an increase in the proportion of cases among foreign-born persons, and an increase in the proportion of Asians among persons with XDR-TB, compared with 1993-1999.

Rates of INH or RIF resistance alone in U.S. cases of confirmed TB in 2007, the most recent year for which complete drug-susceptibility data are available, are not provided by

¹⁵ Iseman M. Treatment and implications of multidrug-resistant tuberculosis for the 21st century. *Chemotherapy* 1999;45(suppl 2):34-40.

¹⁶ Cauthen GM, Kilburn JO, Kelly GD, et al. Resistance to antituberculosis drugs in patients with and without prior treatment: survey of 31 state and large city laboratories, 1982-1986. *Am Rev Respir Dis* 1988;137:Suppl:260

¹⁷ Iseman M. Treatment and implications of multidrug-resistant tuberculosis for the 21st century. *Chemotherapy* 1999;45(suppl 2):34-40.

¹⁸ CDC. Extensively drug-resistant tuberculosis—United States, 1993-2006. *MMWR* March 23, 2007;56(11):250-3.

the CDC, but the percentage of TB cases overall with resistance to INH and RIF (MDR-TB) is 1.2% (125/10,190), as noted above in Section 3.2.2 “United States Epidemiology.”

4. Endpoints

Endpoints are distinct and measurable characteristics used in clinical studies to assess the outcome of therapeutic interventions. One of the primary clinical endpoints of interest in trials of both drug-susceptible and MDR-TB has been clinical cure, or absence of disease relapse. However, the long duration of MDR-TB treatment of a minimum of 18 months requires the consideration of early endpoints in clinical trials to facilitate drug development.

An early endpoint must meet several requirements. First, the endpoint should correlate with treatment outcome. Several endpoints have been used in clinical trials of drug-susceptible TB which could potentially qualify as useful early endpoints in trials of MDR-TB, and can be generally divided into microbiologic (EBA, sputum smear, sputum culture conversion, serial colony counts, time to sputum culture conversion), and clinical endpoints. Second, timing of the endpoint is also important, since drug therapy in tuberculosis, including MDR-TB, consists of two phases. The initial or intensive early phase involves administration of drugs that possess good bactericidal activity to produce an early and rapid decrease in the viable bacterial count.¹⁹ Regimens with poor bactericidal activity fail to clear sputum of AFB, resulting in early treatment failure. However, equally important is the subsequent continuation or consolidation phase of therapy, which involves killing of residual mycobacteria in slowly metabolizing populations that may be sequestered in different anatomical compartments. These populations can potentially lead to the development of late disease relapse if they are not eradicated, since early termination of effective drug therapy leads to regrowth of these residual mycobacteria.

Much of the published data provides information on these early endpoints in relation to drug-susceptible TB, including the time frame relative to treatment and follow-up when these endpoints were measured. To facilitate discussion as to whether these endpoints are suitable for MDR-TB, including whether these endpoints and the timing of these endpoints are similar to what has been reported for drug-susceptible TB, publications specifically addressing MDR-TB have been identified and summarized within this document.

This section of the document begins by describing endpoints used in TB clinical trials which could serve as potential early endpoints to predict long-term treatment outcome, and ends by examining the correlation of the described early endpoints as predictors of treatment outcome (i.e., relapse) using a review of the literature.

4.1. Early Endpoints

¹⁹ Perrin FM, Lipman MCI, McHugh TD, Gillespie SH. Biomarkers of treatment response in clinical trials of novel antituberculosis agents. *Lancet Infect Dis* 2007;7:481-90

4.1.1. Microbiological Endpoints

4.1.1.1. Early Bactericidal Activity (EBA) Studies

Early bactericidal activity (EBA) trials are often the initial studies that are conducted in the investigation of new TB drugs. EBA trials allow for comparison between individuals TB drugs, and produce the results that are most clear in patients with presumed drug-susceptible TB infection without previous treatment.

In EBA studies, newly diagnosed patients with sputum positive pulmonary TB are treated for periods ranging from 2 to 14 days with single drugs or drug combinations. During this period, quantitative counts of viable tubercle bacilli from collected sputum specimens are made, with the EBA traditionally expressed as log-decrease in colony forming units/ml sputum/day over the first 48 hours.²⁰

The first EBA study was conducted by Jindani et al (1980) in Kenya.²¹ Counts of colony-forming units of *M. tuberculosis* were carried out on selective medium during the first two weeks of treatment of 124 patients with newly diagnosed pulmonary TB. Twenty-seven different chemotherapy regimens were studied, and these included daily administration of thiacetazone, *p*-aminosalicylic acid, pyrazinamide, rifampin, streptomycin, ethambutol, and isoniazid alone, and certain 2-drug, 3-drug, and 4-drug combinations. Examination of the separate results of the colony counts in each treatment series showed that there was an initial rapid fall in counts during the first two days of treatment, followed by a slower fall during the remaining 12 days of the 14-day treatment period.

EBA studies do have significant utility. Quantitative sputum microbiology and pharmacokinetics serve as the primary endpoints in such trials, and the results are obtained quickly, as the trials are usually short (7 to 14 days exposure) and involve only a few patients (4 to 25 per arm). They allow comparison of bactericidal activity between individual TB drugs at differing doses, and between new drugs or agents in the same drug class.

However, EBA studies do not allow for assessment of sterilizing activity, and are therefore not an appropriate endpoint for late treatment outcome endpoints such as TB relapse. In addition, the duration of the EBA study may influence the results obtained; a study that lasts two days will lose potentially important information about a drug regimen that is given for longer than this time period. That said, there is no consensus in the literature on what the optimum duration of such a study should be, with study lengths

²⁰ O'Brien RJ. Studies of the early bactericidal activity of new drugs for tuberculosis: a help or a hindrance to antituberculosis drug development? *Am J Crit Care Med* 2002;166(1):3-4

²¹ Jindani A, Aber VR, Edwards EA, Mitchison DA. The early bactericidal activity of drugs in patients with pulmonary tuberculosis. *Am Rev Respir Dis* 1980;121(6):939-49

varying from two to seven days.²² Lastly, it should be noted that even short-course monotherapy (e.g., 2 to 14 days of exposure) may result in the development of resistance to an experimental drug and may also lead to subsequent disease progression. For this reason, enrollment has generally been limited to immunocompetent, treatment-naïve adult patients at low risk of drug resistance and extrapulmonary disease. As a result, EBA studies are therefore not appropriate for MDR-TB trials.

4.1.1.2. Sputum Smear

The quantification of changes in bacillary counts on microscopic examination of sputum preparations is often used as a marker of treatment response in TB trials. This method of diagnosis is feasible in resource-limited settings, and is quick to perform, with results becoming available within hours, as compared to several weeks with sputum culture.

Rieder (1996) evaluated the cumulative frequency of sputum smear conversion examined by direct microscopy by month of treatment in a cohort of 231 patients with sputum smear-positive TB in Thailand.²³ The treatment regimen comprised six months of daily RIF plus INH, supplemented by PZA plus SM during the first two months. Three early morning sputum samples were obtained on consecutive days for each patient for as long as the patient remained on treatment, and these were graded depending upon the burden of AFB seen microscopically. Each month, a mean score was calculated (mean score of $\geq 2+$ was designated as strongly positive; $1+$ to $< 2+$ was moderately positive; $< 1+$ but positive was weakly positive; and 0 was negative). As shown in the table below, 89 (38.5%) had strongly positive smears, 83 (35.9%) moderately positive smears, and 59 (25.5%) weakly positive smears at diagnosis.

Treatment outcome in 231 patients with sputum smear-positive tuberculosis, by month of treatment, Khao-I-Dang, Thailand, 1981-1984

Adapted from Rieder HL, Tuberc Lung Dis 1996;77:126

Month	No. of patients with smear score available					Cumulative no. of patients lost			
	Negative	Weak	Moderate	Strong	Total	Died	Transferred	LTF†	Total
At diagnosis	0	59	83	89	231	0	0	0	0
End of 1st mo	126	47	36	8	217	5	5	3	13
End of 2nd mo	153	37	14	0	204	6	12	9	27
End of 3rd mo	167	20	5	1	193	6	21	11	38
End of 4th mo	168	13	1	1	183	6	28	14	48
End of 5th mo	170	5	2	1	178	6	33	14	53
End of 6th mo	168	7	1	0	176	7	34	14	55

²² Perrin FM, Lipman MCI, McHugh TD, Gillespie SH. Biomarkers of treatment response in clinical trials of novel antituberculosis agents. *Lancet Infect Dis* 2007;7:481-90

²³ Rieder HL. Sputum smear conversion during directly observed treatment for tuberculosis. *Tuberc and Lung Dis* 1996;77:124-129

*1 additional patient had no result recorded at the end of the first month.

†LTF = Loss-To-Follow-up (Absconded)

Rieder HL, *Tuberc Lung Dis*1996;77:126, page 126.

As shown in the figure above, by the end of the 2-month intensive phase, 90.9% of patients with weakly positive smears had converted to negative, as had 77.9% of patients with moderately positive smears, and 61.7% of patients with strongly positive smears. Of all patients combined, conversion was 75% after 2 months, and 95.5% after 6 months of directly observed treatment.

In an analysis excluding 55 patients who died, were transferred to another camp, or absconded, the finding of any positive smear at 2 months was very strongly predictive for a positive smear at 4 months or later [adjusted OR 4.2, 95% confidence interval (1.5, 11.4), $p = 0.005$].

The study concluded that a positive sputum smear result at 2 months strongly predicted smear results after 4 months, and that the correlation between smears and cultures was generally good. The 2-month culture result was thought to be a good predictor for the final outcome of the patient beyond treatment completion. The authors also concluded that the probability of relapse was likely highest in those with the highest 2-month bacillary load. These results supported the notion that patients with a single positive smear after 2 months of treatment could benefit from prolongation of the intensive phase.

Despite the findings of Rieder's study and others, several issues limit the usefulness of sputum smear as a viable early endpoint. A minimum of 5000 to 10,000 AFB per μL of sputum sample is needed for bacterial detection.²⁴ This becomes problematic in patients who produce little sputum, or who have a low sputum bacterial burden. Twenty-five to 50% of suspected pulmonary cases of TB are smear-negative at diagnosis,²⁵ and AFB smear examination possesses a sensitivity of only 50% to 60%,²⁶ a value that is largely dependent upon the skill of the observer. In addition, sputum smear examination is unable to distinguish between *M. tuberculosis* and non-tuberculous mycobacteria, or between viable and non-viable organisms.²⁷ Based on these limitations, sputum smear examination may not be a suitable endpoint for the study of TB in drug trials, particularly when other methods are available.

4.1.1.3. Serial Sputum Colony Counts

²⁴ Parry CM. Sputum smear negative pulmonary tuberculosis, *Trop Doct* 1993;23:145–146

²⁵ Kim TC, Blackman RS, Heatwole KM, Kim T, Rochester DF. Acid-fast bacilli in sputum smears of patients with pulmonary tuberculosis: prevalence and significance of negative smears pretreatment and positive smears post-treatment, *Am Rev Respir Dis* 1984;129:264–268

²⁶ Siddiqi K, Lambert M-K, Walley J. Clinical diagnosis of smear-negative pulmonary tuberculosis in low-income countries: the current evidence. *Lancet Infect Dis* 2003;3(5):288-96

²⁷ Hobby GL, Iseman MD, Holman AP, Jones JM. Enumeration of tubercle bacilli in sputum of patients with pulmonary tuberculosis. *Antimicrob Agents Chemother* 1973;4:94-104

Mean daily serial sputum colony counts over 28 days or longer have been proposed as mycobacterial markers on the sterilizing activity of drug combinations. By considering a biphasic exponential decay curve as two stages of mycobacterial killing, it is speculated that the first two days assess bactericidal drug activity and the following days assess sterilizing activity. This fall in sputum viable count was suggested to be mainly due to the action of rapidly-acting bactericidal drugs. It is postulated that drugs that act against dormant organisms, or persisters (sterilizing drugs), work slowly and were unlikely to have a significant effect during the first 5 days of observation.

It was subsequently surmised that over longer periods of therapy, if there is more than one population of bacterial cells in the sputum on which drugs act differently, this should be reflected in the equations describing the fall in sputum viable count. There would be one effect representing early bactericidal activity and another reflecting sterilizing activity.

Gillespie et al (2003)²⁸ conducted a study aimed at re-evaluating sputum viable colony counts obtained during the first two months of chemotherapy, and found that their data supported the hypothesis that the decline in sputum viable count of patients treated with two highly active regimens (INH, RIF, PZA, and EMB compared with INH, RIF, and Ciprofloxacin) conformed to an exponential decay with a single phase, rather than a two-phase model. Possible explanations for this unexpected finding included the possibility of a persisting population in the sputum that was not present in sufficient numbers to affect calculation of the single-phase exponential decay curve, or that bacteria responsible for late relapses (the target of sterilizing drugs) are sequestered and do not communicate with the sputum, implying a reason for the failure of anti-TB drugs to penetrate the tissues and kill the organisms.

As stated by Gillespie et al:

It has recently been shown that the sputum viable count of patients receiving monotherapy for short periods (5 days or less) follows a single-phase exponential decay curve.¹¹ This fall in sputum viable count was suggested to be mainly due to the action of rapidly acting bactericidal drugs. It was postulated that drugs that act against dormant organisms, or persisters (sterilising drugs), work slowly and were unlikely to have a significant effect during the first 5 days of observation. In seeking to extend these observations it was reasoned that over longer periods of therapy, if there is more than one population of bacterial cells in the sputum on which drugs act differently, this should be reflected in the equations describing the fall in sputum viable count; there would be one effect representing early bactericidal activity and another reflecting sterilising activity. This hypothesis is tested in this paper through the re-evaluation of sputum viable counts obtained during the first 2 months of chemotherapy from a previously published clinical trial. The results demonstrate that over this period the fall in sputum viable count is satisfactorily modelled by a single-phase exponential curve. This finding has important implications for our understanding of how to monitor treatment response and the nature of the population of bacterial cells found in sputum. (page 684-685)

²⁸ Gillespie SH, Charalambous BM. A reiterative method for calculating the early bactericidal activity of antituberculosis drugs. *Am J Respir Crit Care Med* 2002;166:31-35

There are at least three explanations for our observation that sputum viable count can be described by a single-phase exponential model. The first is that the earlier models consisting of different populations is not correct, and that we should review the evidence base upon which these theories have been built. However, it is more probable that there is a persisting population in the sputum but that it is not present in sufficient numbers to affect the calculation of the single phase exponential decay curve. Another explanation is the possibility that the bacteria responsible for late relapses—those the sterilising drugs are meant to act on—are not expectorated but are found in a location that does not communicate with the sputum. This would imply that an important reason for late relapse is the failure of anti-tuberculosis drugs to penetrate the tissues to kill the organisms, rather than altered physiological state of the organisms. We cannot speculate on which of these possibilities is correct, but would highlight the need for further studies investigating the physiological state of bacteria present in patients being treated with anti-tuberculosis drugs and more extensive clinical studies to test our mathematical model. Such studies are now underway in our laboratory and at our field site.

Studies on the use of serial sputum colony counts are still ongoing, and all involve drug-susceptible TB. Therefore its applicability as an endpoint in MDR-TB studies is unknown.

4.1.1.4. Time to Sputum Culture Conversion

There are few studies which use time to sputum culture conversion as an endpoint in the MDR-TB literature. Holtz et al. published one of the few studies that specifically used time to sputum culture conversion as an endpoint.²⁹ This study, conducted in Latvia, determined predictors that were associated with the time to sputum culture conversion, and compared these predictors with those previously noted for poor treatment outcomes such as death, treatment default, and treatment failure.

Individually tailored regimens were used to treat the patients, based on the results of in vitro DST obtained before the treatment initiation. The initial regimen consisted of between 4 and 8 drugs, including one injectable (aminoglycoside) and was modified according to the results of second-line DST and included at least 5 drugs to which the patient's TB isolate was susceptible. All treatments were directly observed during the entire course of therapy. Treatment was continued for 12 to 18 months, depending on the severity of lung disease, history of treatment for TB, and general response to treatment. After treatment was completed, patients were followed for 2 years with sputum testing done every 6 months.

The initial time to sputum culture conversion was calculated as the interval in days between the date of treatment initiation for MDR-TB and the collection date of the first of 2 consecutive negative sputum cultures. Among all patients, the median time to initial sputum culture conversion was 83 days (see figure below). Among the 129 patients who achieved sputum culture conversion, the median time to conversion was 60 days (range, 4 to 462 days). Ninety of the 167 subjects with a positive sputum culture also had sputum

²⁹ Holtz TH, et al. Time to Sputum Culture Conversion in Multidrug-Resistant Tuberculosis: Predictors and Relationship to Treatment Outcome. *Ann Intern Med* 2006;144:650-659.

smear positivity. These subjects had similar rates of conversion and time to conversion as the 167 subjects.

Initial sputum culture conversion in 129 of 167 culture-positive patients who had culture conversion
Holtz, Ann Intern Med 2006;144:653

On univariate analysis among the 129 patients who converted, longer initial sputum culture conversion times were associated with a high colony count (3+ or 4+) on initial culture (83 days vs. 47 days; $p = 0.010$); requiring surgical management during treatment (173 days vs. 56 days; $p = 0.001$); and the use of thiacetazone (69 days vs. 42 days; $p = 0.047$), PAS (71 days vs. 56 days; $p = 0.008$), or cycloserine for 3 months or more (68 days vs. 47 days; $p = 0.02$).

The median initial sputum culture conversion time among those who were cured or completed treatment versus those with a poor outcome was 48 days vs. 169 days, respectively ($p = 0.001$). In 2 years of follow-up after treatment completion of the 129 patients who ultimately had sputum culture conversion, 108 (84%) achieved a good outcome, 5 died (4%), 14 had treatment default (11%), and 2 had treatment failure (1%) (see table below). While among the 38 patients who never had sputum culture conversion, 8 died (21%), 4 had treatment default (11%), and 26 had treatment failure (68%). Three (2%) patients required retreatment for MDR-TB. The proportion of subjects achieving a good treatment outcome in the 2 years of follow-up was 96% for patients with initial sputum culture conversion within 1 month, 86% for patients with initial sputum culture conversion within 60 days (2 months) of treatment, 85% for those subjects with initial sputum culture conversion within 4 months or within 6 months, and 83% for patients with initial culture conversion by 8 months. Those who did not convert were automatically considered as not having a good outcome.

Initial Sputum Culture Conversion and Outcome of Treatment among 167 Patients with MDR-TB*
Holtz, Ann Intern Med 2006;144:653

Time Sputum Conversion Occurred	Patients N	Final Outcome, n (%)*				
		Cured	Completion of Treatment	Death	Default†	Treatment Failed
<1 mo	27	24 (89)	2 (7)	0 (0)	1 (4)	0 (0)
Within 1-2 mo	38	29 (76)	1 (3)	2 (5)	5 (13)	1 (3)
Within 2-4 mo	36	30 (83)	0 (0)	1 (3)	5 (14)	0 (0)
Within 4-6 mo	12	9 (76)	1 (8)	1 (8)	1 (8)	0 (0)
Within 6-8 mo	7	4 (57)	0 (0)	1 (14)	2 (29)	0 (0)
>8 mo	9	8 (89)	0 (0)	0 (0)	0 (0)	1 (11)
Did not convert	38	0 (0)	0 (0)	8 (21)	4 (11)	26 (68)

*Values may not add up to 100% because of rounding

† Treatment default was considered to have occurred in patients who interrupted treatment for 2 or more consecutive months

In summary, 77% of the 167 Latvian patients with pulmonary MDR-TB and sputum mycobacterial cultures positive for *M. tuberculosis* who initiated treatment in 2000 under the DOTS-Plus strategy achieved sputum conversion. About half of the patients converted within 12 weeks and among those who converted, the median time to

conversion was 8 weeks. The study concluded that patients who achieved earlier sputum culture conversion were more likely to have successful treatment outcomes and reported that treatment outcomes were statistically significantly worse for patients with MDR-TB who did not have sputum culture conversion within 2 months.

The study had several limitations. Monthly sputum cultures were not performed in every patient, as they should have been according to the DOTS-Plus strategy. In addition, because cultures were done monthly, the actual number of days to conversion was not observed although the rates of good outcome by time to sputum culture conversion were fairly constant.

4.1.1.5. Sputum Culture Conversion

Sputum culture conversion status after two months of TB treatment is currently the endpoint for which there is the most experience as a predictor of non-relapsing cure for drug-susceptible TB.³⁰ Data on sputum smear conversion in MDR-TB will be presented after a brief summary on the data available on this endpoint in drug-susceptible TB.

Use in Drug-susceptible TB

Wallis et Al. summarized the data that exist in the literature for 2-month sputum culture conversion in relation to relapse in drug-susceptible TB.³¹ As shown in the table below, sputum culture conversion was examined at three levels: across trials, within trials, and at the level of individual patients. An inverse relationship was found to exist between 2 month conversion and relapse rates across trials, i.e., the higher the 2-month sputum conversion rate, the lower the relapse rate. This relationship became more significant once the data within studies were examined, with the addition of new drugs to regimens having incremental effects (see figure below).

³⁰ Mitchison DA. Assessment of new sterilising drugs for treating pulmonary tuberculosis by culture at 2 months. *Am Rev Respir Dis* 1993;147:1062-63

³¹ Wallis RS, Doherty TM, Onjebujoh P, Vahedi M, Laang H, Olesen O, Parida S, Zumla A. Biomarkers for tuberculosis disease activity, cure and relapse. *Lancet Infect Dis* 2009;9:162-72

Relationship between sputum culture conversion and relapse

Wallis RS, Doherty TM, Onjebujoh P, Vahedi M, Laang H, Olesen O, Parida S, Zumla A. Biomarkers for tuberculosis disease activity, cure and relapse. *Lancet Infect Dis* 2009;9:162-7, page 163.

Relationship between change in 2-month sputum culture conversion and relapse rates due to new drug addition to tuberculosis regimen

Wallis RS et al, *Lancet Infect Dis* 2009;9:164

Tuberculosis regimen new drug added to : Hong Kong: E and Z added to SHR; E. Africa (purple circle): Z added to SHR; India: R added to SHZ ; E. Africa (violet square) : Z added to SHR ; E. Africa (pink triangle): Z and R added to SH

Mitchison (1993) compiled data from seven studies that compared different treatment regimens for drug-susceptible TB, with follow-up of up to two years (see table below). Note that many of these studies were also reported in the paper by Wallis et al.²⁶ The table lists the culture conversion results at 1, 2, and 3 months and the relapse rate, which was usually reported at 2 years after the end of chemotherapy. These studies explored regimens where single drugs (RIF or PZA) were added either to a basic SM and INH regimen (study 1) or to the other drug combinations (studies 2-5), or where the non-sterilizing drug EMB replaced PZA (studies 6 and 7).

Culture results at 1, 2, and 3 months after the start of chemotherapy related to the subsequent relapse rate

Mitchison DA. *Assessment of new sterilising drugs for treating pulmonary tuberculosis by culture at 2 months. Am Rev Respir Dis* 1993;147:1062-63, page 162.

Examination of these results demonstrated that in the majority of these regimens, sputum culture conversion at 3 months was greater than 90%, while differences between regimens was still present at 2 months. For example, in Study 7, the 2SHRZ regimen had a lower relapse rate than the 2SHRE regimen (7% vs. 23%). The 2-month sputum culture conversion rate was 95% and 81% respectively, suggesting good correlation between ability to convert at 2 months and longterm treatment outcome. The sputum culture conversion rate at 3 months, however, was non-discriminatory, as sputum conversion was high in both treatment arms. The authors concluded that there was good evidence that 2-month sputum conversion was a reliable measure of sterilizing activity and relapse, and could be used as an indicator of efficacy long before ultimate relapse rates were known.

Use in MDR-TB

Sputum culture conversion is the most commonly used endpoint to date in MDR-TB trials. However, the overall limited quantity of data compared to that of drug-susceptible TB makes it difficult to determine if the predictive relationship seen between 2-month sputum culture conversion and relapse in drug-susceptible TB indeed holds for MDR-TB. Furthermore, the optimal timing of this early endpoint is also in question, with one publication which summarized eight MDR-TB outcome studies showing a median interval to culture conversion exceeding 2 months.³² As the Mitchison results described earlier in drug-susceptible TB clearly demonstrate, timing of the endpoint can be as

³² Sacks LV, Behrman RE. Developing new drugs for the treatment of drug-resistant tuberculosis: a regulatory perspective. *Tuberculosis (Edinb)*. 2008; 88Suppl 1:S93-100.

important as choice of the endpoint itself. While promising, the role of sputum culture conversion as an early endpoint to predict relapse requires further study.

4.1.2. Clinical Endpoints

In early TB trials, most of which evaluated treatment in drug-susceptible TB, clinical endpoints such as resolution of fever, decreased sputum production and weight gain were used in conjunction with radiologic improvement and sputum culture conversion to demonstrate efficacy of drugs with purported activity against *M. tuberculosis*. With the development of highly effective combination therapy for drug-susceptible TB, the objectives of modern TB trials have shifted, and focus now on treatment shortening and preventing the emergence of drug resistance. As a result, clinical endpoints of active disease and resolution of signs and symptoms of disease have not been routinely employed and/or systematically collected in modern clinical trials. There is a relationship between the rate of relapse and the ability of a regimen to convert sputum cultures to negative after 2 months of therapy in the drug-susceptible TB literature.³³ If a relationship exists between sputum culture conversion and clinical resolution of signs and symptoms of disease, then clinical endpoints could have potential use as early endpoints predictive of treatment outcome as well. As previously discussed, however, the relationship between sputum culture conversion and relapse has not been systematically or extensively studied in MDR-TB as compared to drug-susceptible TB; furthermore, sputum clearance and its correlation with clinical resolution of signs and symptoms has also not been systematically studied in the MDR-TB population. Nonetheless, it is still useful to determine the presence and strength of a correlation between sputum clearance and resolution of clinical symptoms in drug-susceptible TB to determine the potential role, if any, of clinical endpoints in future MDR-TB studies.

The table below shows the relationship between sputum clearance at a specific time point, and corresponding clinical endpoints in early drug-susceptible TB studies performed by the Medical Research Council (MRC) and the United States Public Health Service (USPHS) in the investigation of streptomycin³⁴ and isoniazid.^{35,36} In all studies, there was a trend toward better clinical outcomes, such as temperature decrease in patients febrile at enrollment, weight increase in patients underweight at enrollment, and positive change in clinical condition as assessed by the physician in charge, in patients with greater sputum clearance at the defined endpoint. For example, in the MRC study of INH in 1953, patients randomized to receive the combination of INH plus SM had the highest proportion of sputum clearance at 3 months (67%) compared to the other

³³ Burman WJ, Goldberg S, Johnson JL, et al. Moxifloxacin versus Ethambutol in the first 2 months of treatment for pulmonary tuberculosis. *Am J Respir Crit Care Med* 2006;174:331-8.

³⁴ Anonymous. Streptomycin treatment of pulmonary tuberculosis; a medical research council investigation. *Br Med J* 1948; 1(4582):769-82.

³⁵ Anonymous. Isoniazid in the treatment of pulmonary tuberculosis; second report to the Medical Research Council by their Tuberculosis Chemotherapy Trials Committee. *Br Med J* 1953; 1(4809):521-36.

³⁶ Chapman PT. Control study of isoniazid, a United States Public Health Service cooperative investigation. *Trans Annu Meet Natl Tuberc Assoc* 1953;49:437-42.

treatment arms, and also had better clinical outcomes with respect to temperature, weight change, and general condition improvement compared to the other treatment groups. This group also had greater positive changes in the laboratory and imaging endpoints (baseline elevated ESR and radiographic changes) compared to the other groups.

Sputum clearance and associated clinical, laboratory and radiologic endpoints in drug-susceptible TB trials of streptomycin and isoniazid

Study	Drug	Clinical endpoints						
		Time point	Sputum clearance	Temperature change (fever resolution)	Weight change (increase)	“General condition”	ESR change*	Radiologic improvement (slight to considerable)
MRC study of SM, 1948	SM x 4 months (n=55)	6 month	15%	46%	47%	N/A	32%	69% of which 51% was considerable improvement
	Bedrest (n=52)		4%	28%	38%		8%	33% of which 8% was considerable improvement
MRC study of INH, 1953	INH (n=120)	3 month	37%	68%	94%	78%	25%	54%
	INH+SM (n=142)		67%	82%	96%	87%	45%	64%
	SM +PAS (n=102)		55%	76%	78%	75%	21%	64%
USPHS study of INH, 1953	INH (n=205)	Sputum time point: mean for weeks 16-40	56%	80% in all groups	Weight normal in 45% of all underweight patients	N/A	N/A	50%
	INH+SM (n=195)		75%					59%
	SM +PAS (n=183)	Clinical time point: weeks 32-40	60%					51%
		Radiologic: 40 weeks						

*ESR elevated at baseline (>21) and normal (<10) at specified time point

In the evaluation of ethambutol in the re-treatment of cases of pulmonary TB, Donomae et al. studied patients who had not responded to therapy with primary antituberculous drugs with cavitation on chest radiograph and whose microbiologic cultures showed resistance to streptomycin and isoniazid.³⁷ The results of this study are potentially more relevant than the results of the MRC and USPHS studies in the above table, as this population more closely simulates an MDR-TB population.

³⁷ Donomae I, Yamamoto K. Clinical evaluation of ethambutol in pulmonary tuberculosis. Ann N Y Acad Sci 1966;135 (2):849-81.

The table below shows the effects on clinical symptoms, ESR and radiographic changes in re-treatment cases of streptomycin and isoniazid resistant pulmonary TB. One hundred and forty-one cases were divided at random into three groups (ethambutol 1g QD, ethambutol 1g every other day, and a control arm of conventional drug regimens which were combination regimens which did not include ethambutol). Unlike the results obtained at 3 months in the MRC study of INH, where combination therapy was better than monotherapy for both microbiologic and clinical endpoints, such a relationship was not seen with this study. Thus while the 2 month sputum conversion rate was greater for E 1g QD compared to E 1g every other day and conventional drug treatment, and improvement of cough was seen in a higher percentage of patients, resolution of fever and increase in body weight was lower in the E 1g QD group, compared to the other groups. It is noted that the Donomae study examined clinical endpoints at 2 months, while the MRC study time point was 3 months, and it may simply be that the 2 month time point was too early to establish a clear relationship between sputum clearance and clinical symptoms. Assessment of symptoms, such as absence of a cough and resolution of fever are routinely used to make decisions regarding discontinuation of respiratory isolation and general “response to therapy” in the clinical setting. However, the absence of a direct relationship between sputum clearance and the clinical endpoints examined in the Donomae study demonstrate the limitations of using these 2 month clinical endpoints in clinical trials of patients with tuberculosis not responsive to streptomycin and isoniazid.

Sputum clearance and associated clinical, laboratory and radiologic endpoints in the re-treatment of patients resistant to streptomycin and isoniazid with ethambutol monotherapy and combination therapy

Adapted from Donomae I, Yamamoto K. Clinical evaluation of ethambutol in pulmonary tuberculosis. Ann N Y Acad Sci 1966;135 (2):849-81.

Study	Drug	Time point	Sputum clearance	Temperature change (fever resolution)	Weight change (increase)	Decreased cough	Decreased sputum production	Increased appetite	ESR change	Radiologic improvement in patients with no cavitation*	Radiologic improvement in patients with cavitation**
Donomae and Yamamoto, 1966	E 1g QD (n=49)	2 month	50%	46.2%	6.2%	42.6%	38.3%	20.0%	29.2%	4.2%	16.2%
	E 1g QOD (n=46)		31.2%	63.6%	11.6%	40.5%	40.5%	10.7%	35.3%	0%	10.1%
	Conventional drug regimen (n=46)		23.8%	60%	9.5%	16.2%	21.6%	13.6%	24.2%	4.8%	8.3%

* slightly improved

** markedly, moderately and slightly improved at the end of 6 months

With respect to laboratory markers, studies monitoring responses to TB treatment have shown improvements in erythrocyte sedimentation rate (ESR) and in blood concentrations of acute phase proteins such as C-reactive protein, haptoglobins, ceruloplasmin, α_1 -acid glycoprotein, and β_2 -microglobulin, but over a variable course.²⁵ Such markers have poor sensitivity and specificity, and have not been formally assessed in clinical trials as predictors of relapse. While chest radiography contributes to the initial diagnosis of TB, and mycobacterial load correlates with lung cavitation and extent of disease, radiographic resolution lags behind clinical symptom resolution and is therefore less valuable as a rapid marker for monitoring of treatment.³⁸

In conclusion, early clinical endpoints such as resolution of fever, weight gain and increased appetite are useful in a clinical setting of monitoring response to therapy in patients with drug-susceptible TB. However, poor sensitivity and specificity, and lack of a direct correlation between sputum clearance limit their use as early endpoints in MDR-TB trials. Lastly, it is unclear to what degree, if any, that clinical endpoint data from drug-susceptible populations can be extended to the MDR-TB population.

4.2.Early Endpoints: Predictors of Treatment Outcome

4.2.1. Summary of Published Data in MDR-TB (see also Appendix B for Table of Studies)

In order to assess the timing of early endpoints and correlate early response with treatment outcome, an extensive literature search was conducted. English language publications were sought in the MEDLINE database and Cochrane Library. Search terms included combinations of the words “tuberculosis,” “multi-drug resistance,” “MDR TB,” and “treatment outcomes.” The list of resulting publications was narrowed to studies relevant to our purpose. In addition, references from the publications were also scanned for relevance.

Data were sought on MDR-TB in HIV-positive and -negative individuals. The search using the terms previously cited revealed a small number of papers pertinent to HIV infection in MDR-TB patients. These same search terms were combined with the terms “HIV,” or “AIDS” in order to identify more papers. Approximately 71 papers were reviewed, of which 22 were considered relevant for this analysis. **Appendix C contains the bibliography for these studies.**

Information that was considered relevant to our purpose included the following:

- Type of study (retrospective or prospective)

³⁸ Perrin FM, Lipman MCI, McHugh TD, Gillespie SH. Biomarkers of treatment response in clinical trials of novel antituberculosis agents. *Lancet Infect Dis* 2007;7:481-90

- Resistance pattern (i.e. resistance to INH and RIF, and/or to more drugs)
- Nature of drug treatment regimen (standardized or individualized; inclusion of fluoroquinolones or not, etc)
- Duration of treatment
- Rate of sputum smear and culture conversion
- Timing of sputum smear and culture conversion
- Clinical signs/symptoms, and time to resolution of these factors
- Rate of relapse, and time to relapse
- Duration of follow-up after treatment completion
- Mortality rate (all-cause and TB-related mortality)

These factors were summarized in tables according to HIV status, where the majority of studies enrolled HIV-negative subjects. Stratification on the basis of HIV status was deemed relevant since important differences in these populations can affect treatment outcomes.³⁹ These include the potential for drug interactions (particularly between rifamycins and ARVs), paradoxical reactions that may be interpreted as clinical worsening, and the potential for the development of acquired resistance to rifamycins when treated with highly intermittent therapy.

See Appendix A for Table of Data on HIV-Negative Subjects from Published Trials of MDR-TB

See Appendix B for Table of Data on HIV-Positive Subjects from Published Trials of MDR-TB

See Appendix C for Bibliography of References

From the resulting table of HIV-negative subjects (Appendix A), several observations and conclusions were made. Trial characteristics were very heterogeneous, which led to significant variation in the outcomes that were assessed. The comparisons made here are for the purpose of delineating any noticeable similarities, differences, and trends in the data, in order to best assist in the goal of designing clinical trials for new drugs for MDR-TB. The FDA's conclusions for HIV-negative patients were as follows:

Location of Study: Most studies were conducted outside the United States, where the burden of MDR-TB is greatest. Two studies were conducted in South Africa, two in Peru, two in Korea, and three in the United States. One study was carried out in each of the following countries/territories: Argentina, Hong Kong, Indonesia, Taiwan, The Netherlands, and Turkey. One multi-site study recruited and followed patients in Estonia, Latvia, Peru (Lima), the Philippines (Manila), and the Russian Federation (Tomsk).

It is difficult to control for all the variables that are inherent in conducting studies in countries other than the U.S., assuming that the regulating authorities are located in the U.S. countries have their own NTPs, and drug regimens that are recommended for

³⁹ Centers for Disease Control and Prevention. Treatment of tuberculosis, American Thoracic Society, CDC, and Infectious Diseases Society of America. MMWR 2003;52(No. RR-11):1-80

treating MDR-TB. The WHO Guidelines are often seen as the guiding authority in constructing these national guidelines, but the latter often depend upon local resistance patterns, availability of drugs, and other such factors. Specific local factors may also play a role in one country, but not in another. As such, these differences between countries must be kept in mind when designing MDR-TB trials, and ways must be sought to account for them.

Type of Study: Eleven studies were conducted retrospectively, while five were prospectively conducted. The retrospective trials utilized patient data taken from multiple sources, such as medical records and national TB patient registers; none of the trials had a case/control design. One of the most significant disadvantages of the design of these retrospective trials was the fact that patients were not randomly assigned to treatment groups, which makes it difficult to form definitive conclusions on certain associations. This study design may arguably be the most straight-forward and efficient for a relatively uncommon outcome like MDR-TB.

Prospective studies require that patients be followed for several years to obtain adequate data on endpoints, and this method requires many more resources and a longer time period to accomplish. Despite this fact, there were two studies that managed to accrue a large cohort of patients (Nathanson 2006, which enrolled 1,047 patients; and Kim 2001, which enrolled 1,011 patients). Perhaps due to the difficulty of following patients for several years within the context of a study, the other prospectively designed trials each enrolled under 80 patients.

Valuable data can be obtained by randomized, prospective trials, although it is recognized that there are limitations to the accrual of adequate amounts of data, primarily loss-to-follow-up and mortality over time being among them. Ways to overcome such limitations should be sought in the design of MDR-TB trials.

Sample size: A total of just over 5000 patients with MDR-TB were studied, with the majority of trials enrolling over 100 eligible patients. The smallest trial (Suo 1996) followed 17 patients, while the largest (Nathanson 2006) followed 1,047 patients. Drawing conclusions from small studies is problematic; the full spectrum of disease may not be seen in these few patients, and losses from the cohort, or deaths, may have large effects on the outcomes that are measured. Given the relatively modest numbers of patients with MDR-TB in most countries it may be prudent to recruit in multiple sites in order to obtain an adequate sample size for a study, as was done in the Nathanson and Kim studies. These efforts can be hampered, however, by local differences in therapeutic standards, resources, belief systems, and the like. Such factors must be controlled for as much as possible if the goal is to obtain robust data from as many suitable patients as possible.

Demographics: Basic patient characteristics like age and gender were presented in all the papers. The majority of patients studied were between 30 and 50 years of age, the working-age population, which reflects where the burden of MDR-TB may lie in most countries. There were relatively few children with MDR-TB who were studied, and even

they were mostly above the age of 10 years. TB in children manifests differently than it does in adolescents and in adults, and the management differs as well. Age should therefore be a consideration in recruitment for MDR-TB trials, as it appears to have been in the prospective trials (the youngest patient noted was 11.8 years).

Disease characteristics: Characteristics of TB disease were not routinely reported in the trials that were reviewed. The factors that were most often (but not universally) discussed included: radiographic findings, in terms of the extent of disease (number of cavities); the presence of EPTB; and the performing of surgical intervention in the management of patients. Mitnick (2003), for example, reported that 47 of 75 patients (63%) had bilateral cavities on chest radiography. Tahaoglu (2001) reported that 152 of 158 patients (96%) had at least one cavity on chest radiography, while extensive disease was noted in 63 of 158 patients (40%), and limited disease was seen in 95 of 158 patients (60%). Cavitation and/or extent of lung disease were reported also by Goble (1993), Telzak (1995), Park (1998), Geerlings (2000), and Chan (2004). Several studies state that patients had surgical procedures (Goble, Tahaoglu, Chan, Palermo (2004), and Nathanson), while no such data are provided for five studies, namely Hadiarto (1996), Schaaf (1996), Suo (1996), Kim (2001), and Suarez (2002). Only Park (1998) discusses initial clinical symptoms of the patients who were recruited, including fever, pulmonary complaints and constitutional symptoms. These clinical factors are important to collect at the initiation of the study as they can be followed for resolution, and provide support for the microbiological endpoints that are obtained in drug trials for MDR-TB. These endpoints are bolstered by findings of a resolution in clinical symptoms with TB treatment.

Resistance: All the studies gave information on the mean or median number of drugs to which the patients were resistant; the range was 2.0 to 6.0 drugs.

There did not appear to be a proportional relation between numbers of drugs to which a patient's isolate was resistant and late endpoints such as relapse or failure. For example, the patients in the Goble (1993) trial had isolates with resistance to a median of 6 drugs (high in relation to the other studies), and the relapse rate was 14% (12 of 87 patients), and failure rate 35% (47 out of 171 patients). The Suo study (1996) had patients with isolates that were resistant to a mean of 4.4 drugs (mid-range for these studies), but the relapse rate was higher than that of the Goble study, at 27% (4 of 15 patients), while the failure rate was lower at 24% (4 of 17 patients). The Kim study (2001), on the other hand, had patients with isolates having a mean resistance to 3.7 drugs (low in relation to other studies), but the relapse rate was also low at 2.4% (8 of 335 patients), as was the failure rate at 8.1% (82 of 1,011 patients).

Some individualized drug regimens were based upon the full susceptibility of the *M. tuberculosis* isolate, while others incorporated drugs to which there was partial susceptibility or even resistance. One possible reason for this may have been the differences in available resources for performing DST in the various study host countries, or the lack of available drugs for treatment. The methods for determining susceptibility were also not standard across studies. In some instances, a drug was classified as "susceptible" if it had not been used in a patient's treatment regimen prior to enrollment,

whereas in other studies, patients were included even if they had been taking certain anti-TB drugs for several months. “Partial susceptibility” was defined in the Goble study as there being no growth at the higher concentration tested, or 2% to 33% of the control value for growth at the lowest concentration. The variation in definitions and determinations of susceptibility, therefore, was quite variable across studies.

It is interesting to note that the majority of patients across the studies did not fit into the MDR-TB definition of resistance (i.e., resistance to only INH and RIF). This may have implications for the design of new drug trials in MDR-TB.

Regimen: The majority of drug regimens were individualized (13 of 16 trials), and were based upon the patients’ DST and history of drug treatment. Across the studies, the regimens were comprised of 3 to 8 drugs, usually with at least 3 to which the *M. tuberculosis* isolate was susceptible or to which the patient had not been exposed prior to the trial. Most regimens included at least one parenteral drug (an aminoglycoside or a polypeptide).

There were only 3 trials that used standardized regimens. At the time of the Hadiarto trial (1996), there were no standard policies on the regimen and duration of treatment for MDR-TB, according to this paper. The general recommendation was to use at least 3 other susceptible drugs and perhaps fluoroquinolones. This study used a regimen that included ofloxacin, PZA, EMB and SM. Schaaf (1996) studied patients in South Africa at a time when the standard regimen was INH, RIF, PZA, and SM or EMB. Suarez (2002) described a standard regimen comprising kanamycin, ciprofloxacin, EMB, PZA, and ethionamide. There were not enough trials that used a standardized regimen to compare the outcomes with trials that used individualized regimens.

Considering the design of randomized MDR-TB trials, investigators may decide to use a background regimen (BR, optimized or not) in both arms, with the test arm receiving, in addition, the new drug(s). The decision as to whether the BR should be standardized or optimized is an important one to consider.

Duration of Treatment: The duration of treatment did not vary significantly from one trial to the next, and appeared to be based upon WHO recommendations, in many cases, of treatment for 18-24 months, or 12 months after negative sputum culture conversion. The range among the studies was 9 months to 24 months, with the majority of trials using 18 months of treatment. Hospitalization was taken into account in several trials, and was included in the overall duration of the study.

Duration of treatment must be distinguished from follow-up, which occurs after treatment is completed. Treatment duration appeared to be guided by sputum results, as seen in the ranges around the mean for some of the durations recorded. Kim (2001), for example, found that patients were treated for a mean of 23 months, with a range of 19.6 to 26.4 months. Shean (2006) determined that patients were treated for 17 months, with a range of one to 66 months.

Clinical Signs/Symptoms: Information on resolution of clinical symptoms was not routinely collected in the trials. Only the Telzak trial (1995), in fact, provided any information on resolution of symptoms. The author discovered that TB symptoms (which were not elucidated) resolved in the 17 patients who had a microbiologic response; the timing of this resolution was not provided. Although radiographic data were discussed for patients at enrollment in some studies, the resolution of radiographic findings was not addressed. The lack of clinical information in the setting of treatment made any attempt to associate sputum smear or culture conversion with symptom resolution difficult. During the initial literature search, it was noted that older trials mostly collected these clinical data on patients, while more modern trials usually forego this information for microbiological data only.

As noted in the section above on Disease Characteristics, the validation of an early endpoint should depend not only on microbiologic data, but on clinical data as well. MDR-TB trials which are designed to collect both types of data are more robust than studies that collect only one or the other endpoint.

Completion: The definition of “completion” was not elucidated in every trial, although the results indicated that at times this factor was conflated with “cure.” Due to the fact that explicit information on completion rates was not provided in every trial, it was difficult to assess completion in relation to cure of disease.

Cure: As mentioned above, the definition for “cure” was sometimes unclear. The implication was made that “cure” was synonymous with “completion” in some studies, while in others, “cure” was deemed to be the same as “sputum culture conversion.” Using the designation provided in the papers, cure rates ranged from 33% to 83%, with the mean among the papers reviewed being 53.7%. This figure, much lower than the oft-cited cure rates of over 95% for drug-susceptible TB⁴⁰, reflects the difficulty of successfully treating MDR-TB.

FQs are considered to be the preferred oral agent (specifically levofloxacin) for treatment of drug-resistant TB caused by organisms that are known or suspected to be susceptible to this class of drugs, or when 1st line agents cannot be used due to intolerance. They have significant activity against *M. tuberculosis*. The Global Tuberculosis Control 2009 report of the WHO states that the global goal for successful treatment of new TB cases should be at least 85%⁴¹:

The principal targets [set for 2015] are that the incidence of TB should be falling by 2015 (MDG Target 6.c), that TB prevalence and death rates should be halved by 2015 compared with their level in 1990, that at least 70% of incident smear-positive cases should be detected and treated in DOTS programmes, and that at least 85% of new sputum smear-positive cases should be successfully treated.

⁴⁰ Fox W. Whither short-course chemotherapy? Br J Dis Chest 1981;75:331-357

⁴¹ World Health Organization. Global Tuberculosis Control: epidemiology, strategy, financing. WHO Report 2009. WHO/HTM/TB/2009.411:
http://www.who.int/tb/publications/global_report/2009/pdf/full_report.pdf

According to this document, the targets set in the Global Plan also apply to MDR-TB. The studies assessed in the background document span a time period during which significant changes in management of the disease occurred, despite the paucity in new drug development. FQs are considered to be the preferred oral agent (specifically levofloxacin) for treatment of drug-resistant TB caused by organisms that are known or suspected to be susceptible to this class of drugs, or when 1st line agents cannot be used due to intolerance. The WHO 2008 Guidelines for programmatic management of multidrug-resistant tuberculosis state the following:⁴²

Ciprofloxacin is no longer recommended to treat drug-susceptible or drug-resistant TB. Currently, the most potent available fluoroquinolones in descending order based on in vitro activity and animal studies are: moxifloxacin = gatifloxacin > levofloxacin > ofloxacin. While ofloxacin is commonly used because of relatively lower cost, the later-generation fluoroquinolones, moxifloxacin and levofloxacin, are more effective and have similar adverse effect profiles. Furthermore, the later-generation fluoroquinolones may have some efficacy against ofloxacin-resistant strains. Although similar to moxifloxacin in its efficacy against TB, gatifloxacin is associated with serious cases of hypoglycaemia, hyperglycaemia and new-onset diabetes. If gatifloxacin is used, it should undergo close monitoring and follow-up; gatifloxacin has been removed from the markets of many countries. For this reason, it has not been placed in the tables throughout this guideline. While levofloxacin or moxifloxacin are considered to be more effective against *M. tuberculosis* than ofloxacin, based on animal and EBA data, levofloxacin is, for the time being, the fluoroquinolone of choice until more data confirm the long-term safety of moxifloxacin.

Interestingly, there did not appear to be any association between inclusion of FQs in the treatment regimen, and better cure rates. This observation was also made in the Orenstein meta-analysis (see Section 4.3.1 “Published Meta-Analysis”). It must be noted, however, that the studies were not prospective, nor were they randomized.

Smear conversion: This variable was not routinely assessed in the studies. For the few papers in which this was studied, mean or median time to sputum smear conversion was relatively short (2 to 3 months). It appears from the 2008 WHO TB management guidelines that less emphasis is being placed on sputum smear conversion as a diagnostic criterion. The following statement is taken from the document:

Positive smears with negative cultures may be caused by the presence of dead bacilli and therefore may not indicate treatment failure.

This issue was discussed in Section 4.1.1.2 “Sputum Smear” earlier in this document. Important to note, however, is the fact that sputum smear conversion is often used in resource-limited settings, where culture media and the equipment and skills necessary for interpreting culture results, may not be available outside the context of a clinical trial. However, it may be that the pitfalls of this method of diagnosis and treatment monitoring have pushed investigators to use what is considered the more definitive endpoint, sputum culture, for this purpose.

⁴² World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency Update 2008. Document no. WHO/HTM/TB/2006.402. Geneva: WHO, 2008

Sputum culture conversion: Two factors were assessed with this variable: the sputum culture conversion rate, and the time to conversion. Virtually all the papers provided information on conversion rates, with the majority providing data on both factors. The time to sputum conversion was selected as a specific time point in a minority of papers (i.e. Holtz 2006), while the others collected this information in addition to other early endpoints.

The median or mean time to sputum culture conversion ranged from 35 days to 5 months, with the vast majority of patients converting their sputum culture within 2 months. The Holtz paper found that among the patients who converted their sputum, the median initial sputum culture conversion time was 60 days (range, 4 to 462 days); a figure from that paper shows that the cumulative percentage of patients who achieved conversion starts to level off at approximately 5 to 6 months (see Section 4.1.1.4 “Time to Sputum Culture Conversion”). This suggests that the majority of sputum culture-positive patients with MDR-TB will have converted their sputum to negative by this time point. This is helpful information to have when designing a trial for new drug treatment of MDR-TB.

The overall conversion rates across the trials ranged from 52% to 95% (the latter was an outlier), with the majority being below 80%. These rates were not as low as one might expect for MDR-TB, when only half of the regimens were included FQs. Again, based on the data, one may question the extent of the contribution that FQs have to the regimen, and what outcomes these specifically affect.

Relapse: Information on time to relapse was not provided in most of the papers, while a majority provided some information on rates of relapse. In terms of the number of patients who relapsed, the range was from zero to 50% (latter figure was after 5 years follow-up); the majority of relapses numbered below 10% of those who converted their sputum cultures with treatment.

The time of relapse was not routinely reported in the studies, although several studies reported relapse rates at 2 years, and did not often indicate at what time point between treatment completion and the 2-year mark the relapse rate was assessed. Goble (1993) cited a relapse rate of 14% (12 of 87 patients who had sputum culture conversion) 5 months to 62 months after initiation of treatment. Nine of the 12 patients (75%) relapsed within 2 years. Holtz (2006) reported that by 2 years following treatment completion, 3 of 129 patients (2%) had relapsed. Also using this 2 year time point was Geerlings (2000), who reported a relapse rate of 2.2% (1 of 44 patients). Tahaoglu (2001) reported a relapse rate of 1.3% (1 of 78 patients) at 2 years, while Shean reported relapse rates at 2 years (32 of 281 patients, or 11%) and 5 years (77 of 154 patients, or 50%).

Relapse is an important late endpoint for MDR-TB trials, and is one that may be used to assure adequacy of the initial treatment regimen. One way to confirm that sputum culture conversion translates into long term benefit would be to see a low number of relapsed patients in the treatment arm of a trial that is studying a new drug for MDR-TB. The relative paucity of data on relapse makes this goal a difficult one.

Relapse is an important endpoint that must be considered when assessing the long-term efficacy of a new drug in MDR-TB trials. Demonstration that a drug has a durable effect on clinical outcome, such that the risk and rate of relapse is reduced, improves the robustness of such trials.

Follow-up: The follow-up period for MDR-TB trials is typically long in duration, and the trials reflected this fact. The median or mean follow-up period ranged from 12 months to 5 years, with the majority being approximately 24 months. The wide range in follow-up periods appears to stem from the fact that there are no randomized trials that indicate what the optimum duration of follow-up should be. Late outcomes such as relapse can occur years after one might assume that a patient is cured, making estimation of a specified follow-up period, for the purposes of a study, quite difficult.

Failure: Patients who failed therapy were usually classified as those for whom sputum culture conversion or cure was not achieved. Default patients were not included in this group. Failure rates ranged from 1.5% to 32%, with the majority of trials having a figure of less than 20%. There were only a small number of trials that used a standardized treatment regimen, so data from these trials on failure could not be assessed and compared to those from trials using individualized regimens. One such trial that used a standardized treatment regimen had a failure rate of 13% (Schaaf 1996), while one other had a rate of 32.3% (Suarez 2002), and yet another provided no data on failures (Hadiarto 1996), so the information, as can be seen, was quite divergent.

Failure is an important endpoint in MDR-TB trials. An association between drug regimen, sputum conversion, and failure would assist in showing the long-term benefit of a new drug.

Default (or Loss-To-Follow-up/Absconded): These data were not routinely provided, nor was any distinction made between those who defaulted on treatment and those who absconded. For the purposes of this background document, the figures for all such groups were combined. The default rate ranged from 4.5% to 48%, with the majority being under 25%.

Patients who default or who are lost to follow-up comprise a valuable source of information in MDR-TB trials, such that the results of a trial may be adversely affected if such loss is significant. The conclusions drawn can be affected if patients in a certain study arm, for example, withdraw more than in the other arm. Efforts must be made to insure as much reduction in default or loss-to-follow-up as possible.

Mortality: Information was sought on both all-cause mortality and on TB-related mortality. The majority of papers provided information on the former; fewer papers provided data on those patients who died specifically from MDR-TB. When no differentiation was made by the author(s), the assumption was made that the figures provided referred to all-cause mortality. Assessment of mortality would have required follow-up of patients for long periods of time, and if there was a high level of default or loss-to-follow-up, the figures for mortality of a potentially fatal disease such as MDR-

TB, might be considered to be less than accurate or reliable. The range in all-cause mortality was wide, from 0.3% to 46%. In those trials that provided information on TB-related mortality, the figures ranged from 2.2% to 46%.

Analysis of Published Literature Results

In an attempt to determine which endpoint(s) would be suitable for use in MDR-TB studies as early endpoints predictive of treatment outcome, it was necessary to assess the endpoints that have been studied for drug-susceptible TB. While it was recognized that generalizing endpoint findings from the drug-susceptible TB population to MDR-TB may not be valid, this step was undertaken to first compare and, if similar, strengthen the results obtained in MDR-TB studies, and secondly, to provide information in situations where there was no MDR-TB information.

An appropriate early endpoint should be clinically meaningful and closely associated with disease relapse. EBA studies are not appropriate for new drugs for MDR-TB, as they are inherently too short in duration to assess the sterilizing phase of TB therapy and accordingly, cannot predict the late treatment outcome endpoint of relapse. Furthermore, since this method employs monotherapy with a high risk for the development of drug resistance, it is unethical and inappropriate for use in the MDR-TB patient population. (see Section 4.1.1.1 “Early Bactericidal Activity (EBA) Studies”).

Sputum smear conversion is also not an ideal early endpoint due to poor sensitivity and specificity inherent to the test itself. In addition, data on this endpoint was not routinely collected in the MDR-TB trials that were reviewed, and therefore its ability to predict relapse could not be assessed. Sputum colony counts are not yet widely used by investigators, and the validity of this endpoint is still to be determined. Immunologic and molecular biomarkers (discussed in section 7.4) are still in the early stages of development and study and their potential role as early endpoints is unknown.

From such process of elimination and substantiated by review of the literature, the most widely used early endpoint in both drug-susceptible and MDR-TB trials is sputum culture conversion. The following table summarizes the sputum culture conversion rates (where available), median or mean time of culture conversion, and relapse rate among those who were considered cured/treatment complete in reviewed MDR-TB studies.

The limitations in this compilation of data should be noted from the outset. These values were not routinely reported in full in all the studies, and the papers by Hadiarto (1996), Schaaf (1996), Mitnick (2003), and Nathanson (2006) were left out of the table as a result. The majority of papers reported median time of sputum culture conversion, while others reported the mean; a distinction is made under the table for those papers that report the mean. Ranges for the median or mean time to sputum culture conversion were provided when available. Failure was defined in most studies as persistence of positive cultures (time point at which this was calculated varied). Relapse was similarly assessed at various time points, but data at 2 years were usually reported. For more complete information regarding the figures in the table, readers may refer to the narrative above and to the references in Appendix C.

Sputum Culture Conversion, Time of Culture Conversion, Failure, and Relapse in MDR-TB For HIV-Uninfected Patients (From Literature Review)

Study	Sputum Culture Conversion	Median Time of Culture Conversion (range)	Relapse rate	Failure	Mortality (all-cause/TB-related)
Goble	65% (87/134)	2 mos. (1-8)	14%	35%	37%/22%
Telzak	100% (xx/xx)	69 days (2-705)	0%	0%	4% / No data
Suo	73% (xx/xx)	2 mos.	36%	24%	35% / 12%
Park	82% (52/63)	2 mos. (1-10)*	0%	10%	No data/0%
Geerligs	79% (23/29)	6 weeks (1-20)	3%	0%	14% / 2%
Yew	81% (51/63)	2.1 mos. (1-5)*	2%	14%	No data / 5%
Kim	48% (431/487)	2.1 mos. (1-13)*	2%	8.1%	2% / No data
Tahaoglu	95% (150/158)	1.9 mos. (1-9)*	1%	8%	4% / No data
Suarez	46% (xx/xx)	3 mos.	Unclear	32%	11% / No data
Chan	85% (137/162)	3 mos.	9%	10%	25% / 12%
Palermo	75% (105/141)	5.2 mos. (2.9-7.5)	7%	48%	19.1% / No data
Shean	56% (276/491)	152 days (72-136)	unclear	4%	9% / No data
Holtz	77% (129/167)	83 days (4-462)	11%	1%	8% / No data
Lee	47% (xx/xx)	42 days (mean 48 days)	0%	44%	9%
Chiang	83% 9xx/xx)	6 months (mean 3 mo)	7%	10%	33%/28%
HIV-INFECTED PATIENTS					

*Mean time of culture conversion

The majority of patients studied experienced sputum culture conversion by a median of approximately 2 months, with conversion rates ranging from 56% to 95%. In general, the studies which reported the lowest sputum culture conversion rates (Shean 56%, Goble 65%) also had the highest rates of relapse (11% and 14% respectively) although there were exceptions to this association. Telzak, Suo and Suarez also had sputum culture conversion rates in the mid-60s range, yet reported relapse rates of 0%. Small study size may account for this finding in the Telzak and Suo studies. In the Suarez study, relapse was reported at 18 months, which is shorter than the usual 2 year follow-up period. It is possible that patients were still on therapy at the time of outcome assessment, and relapse could have been observed had patients been followed longer and off therapy. Similarly, the studies which generally reported the higher range of sputum clearance rates (Tahaoglu 95%, Kim 88.5%, Park 82.5%) also had low rates of relapse (1.3%, 2.4% and 0% respectively). Again, an exception was noted with the Chan study. This result can possibly be accounted for by the fact that the study was a retrospective review of patients admitted between 1984-1998, and fluoroquinolones were not routinely used before 1990. Fluoroquinolone use was shown to be moderately related to a favorable response by logistic regression analysis and the authors speculated that a larger patient sample would likely have shown a statistically significant benefit of fluoroquinolones.

The trend for all-cause mortality similarly parallels that of relapse rate, namely the studies which reported the highest relapse rates also tended to report the highest mortality.

Based on the limited quantity of MDR-TB data, these preliminary results suggest that sputum culture conversion can be used to predict the longterm clinical outcome of cure/disease relapse with a reasonable degree of confidence.

4.3. Predictors of Response

The outcome of MDR-TB infection can be affected by several factors independent of the anti-tuberculous drug regimen. A recently published meta-analysis characterized factors associated with good outcome, while radiographic findings and late clinical symptoms in the course of disease resolution may be predictive of poor response. Both of these are briefly described in the following section.

4.3.1. Published Meta-Analysis

In a recently published systematic review and meta-analysis of available therapeutic studies in MDR-TB, Orenstein et al, characterized factors associated with improved treatment outcomes among patients with MDR tuberculosis who were treated with second-line drugs.⁴³ Their analyses assessed the role of individualized versus standardized treatment regimens, characteristics of patients and programs, study settings, and outcome definitions on the reported efficacy of MDR tuberculosis treatment. Of note, only English language publications were considered, which was identified as a limitation of the paper.

In this systematic review and meta-analysis, cure was defined as at least five consecutive negative cultures during the last 12 months of treatment, although as discussed below, the definition of cure ultimately varied amongst the selected studies. Outcomes were required to be reported according to WHO classifications of success (cure and treatment completion), failure, default (treatment interruption), and death, which are listed below. Studies in which all patients had extensively drug-resistant tuberculosis were excluded.

WHO classification:⁴⁴

- **Cured.** A Category IV* patient who has completed treatment according to programme protocol and has at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment. If only one positive culture is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart.

⁴³ Orenstein EW, Basu S, Shah NS, Andrews JR, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. *Lancet Infect Dis* 2009;9:153-61.

⁴⁴ World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency Update 2008. Document no. WHO/HTM/TB/2006.402. Geneva: WHO, 2008: http://www.who.int/tb/publications/global_report/2008/en/

- **Treatment completed.** A Category IV patient who has completed treatment according to programme protocol but does not meet the definition for cure because of lack of bacteriological results (i.e. fewer than five cultures were performed in the final 12 months of treatment).
- **Died.** A Category IV patient who dies for any reason during the course of MDR-TB treatment.
- **Failed.** Treatment will be considered to have failed if two or more of the five cultures recorded in the final 12 months of therapy are positive, or if any one of the final three cultures is positive. (Treatment will also be considered to have failed if a clinical decision has been made to terminate treatment early because of poor clinical or radiological response or adverse events. These latter failures can be indicated separately in order to do subanalysis).
- **Defaulted.** A Category IV patient whose treatment was interrupted for two or more consecutive months for any reason without medical approval.
- **Transferred out.** A Category IV patient who has been transferred to another reporting and recording unit and for whom the treatment outcome is unknown.

*A Category IV patient is defined as suspected or confirmed MDR-TB.

A total of 565 publications were obtained through the literature search. Of these, 33 studies (34 published reports) met the inclusion criteria. The studies were described as follows:

The number of patients previously treated for tuberculosis ranged from 0 to 100% in 30 of the 34 reviewed reports; other studies omitted this statistic. HIV prevalence ranged from 0 to 74% in the 16 studies in which it was reported. The median duration of treatment ranged from 11 months to 25 months. The duration of treatment for individual patients varied widely, with some patients receiving as long as 136 months of therapy based on their culture results and clinical indications. Twenty-one studies reported the length of follow-up after treatment, which often varied between patients within the same study. 16 studies included DOT throughout, 9 maintained DOT during the intensive phase of therapy or directly observed some but not all patients, 6 studies used self-administered therapy, and 3 studies did not report the degree to which treatment was observed. The mean number of drugs used ranged from 3.7 to 8 (median 5.5)... The mean number of drugs to which isolated organisms were resistant ranged from 2.8 to 6.

The definition of cure varied among studies: 14 studies followed the WHO standard definition, which requires at least five negative cultures during the last year of treatment, 7 additional studies required that the patient be culture negative for at least 12 months, and in 12 studies, three or fewer negative cultures were necessary to be classified as “cured”.

Treatment outcomes

The authors report that across all studies that used second-line drugs, the overall treatment success estimate, defined as the proportion of patients who were cured or completed treatment, was 62% (95% CI 58–67%), This estimate was based on pooling across all studies without accounting for variation in study design (e.g. individualized v. standardized treatment programs) and was noted to be potentially biased.

As shown in the Figure below, among the 29 reports of individualized treatment regimens for patients with MDR tuberculosis (mean 268 patients; range 17–1407), the mean proportion of patients achieving treatment success was 64% (95% CI 59–68%). The mean proportion of patients whose outcomes were treatment failure, default, and death were 6%, 12%, and 11%, respectively.

The authors report that among the five studies in which patients with MDR tuberculosis were treated with a standardized regimen (mean 146 patients; range 39–466), the mean proportion achieving treatment success appeared lower than that for individualized treatment at 54% (95% CI 43–68%). However, it is difficult to compare individualized and standardized regimen success rates because of the lack of random assignment of treatment. The mean proportion whose outcomes were failure, default (treatment interruption), and death among the standardized regimen studies were 18%, 12%, and 11%, respectively.

Orenstein EW, Basu S, Shah NS, Andrews JR, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. Lancet Infect Dis 2009;9:153-61.

Studies of individualized and standardized treatment regimens were combined to analyze the effect of each of the other study characteristics independently, as shown in the Table below. This analysis showed that the proportion of patients treated successfully did not differ significantly on the basis of any of the following individual study characteristics: length of treatment, level of direct observation of therapy, regimen design, number of drugs in the regimen, percentage of patients receiving fluoroquinolones, start year of the study, or cure definition. Differences in population characteristics, including prevalence of HIV, mean number of resistant drugs, and proportion of patients previously treated for tuberculosis, also did not lead to significantly different outcomes. Note that given that study designs significantly differed in among studies comprising these sub-groups and that sub-grouping studies based on a single parameter may control for confounding associated with the sub-grouping variable, however, it ignores other potential confounding variables, there is concern that the estimates may be biased.

The authors report that although the proportion of patients achieving treatment success was numerically larger in studies that used individualized treatment regimens, the difference was not significant. In fact, no individual patient or program characteristic was associated with a significantly greater proportion of patients achieving treatment success according to the authors. Studies that incorporated both treatment for longer than 18 months and DOT throughout the entire treatment period had a significantly greater proportion of patients achieving treatment success than all other studies. When treatment programs included both of these factors, 69% (95% CI 64–73%) of patients were successfully treated. Only 58% (95% CI 52–64%) were successfully treated when a maximum of one of the two factors was used. The authors note that substantial heterogeneity in study designs, patient populations, and reporting limited the scope of this analysis.

The authors acknowledge that substantial heterogeneity (high I^2 values) in study characteristics prevents a more conclusive determination of what factors have the most effect on the proportion of patients that achieve treatment success and limits the validity of the analysis. Several studies omitted the exact protocol used in treatment regimen design, length of follow-up, and the average number of drugs to which each patient's TB isolate was resistant. HIV infection was assessed in fewer than half of the studies reviewed. Fluoroquinolone use was only reported in 13 of 34 studies, despite its association within studies with treatment success for MDR tuberculosis.

Therefore, the authors concluded that the lack of significant findings associated with certain variables in the analysis may be due to reporting insufficiency, rather than the absence of a real association.

4.3.2. Late Clinical Symptoms

Initially, resolution of clinical symptoms appears to correlate with sputum clearance. Following sputum conversion and initial cure, reappearance of clinical symptoms should also be part of an assessment of relapse that is based on the total clinical picture, which include sputum examination (if the patient has a recurrence of productive cough), physical examination findings (including chest X-ray), and laboratory tests.

Causes other than pulmonary MDR-TB for the re-appearance of clinical symptoms should be investigated (e.g., extrapulmonary disease, infection with *Mycobacterium avium* complex, acute bacterial pneumonia, HIV infection, hematologic malignancies)

Drug-Susceptible Tuberculosis

Chest radiographic findings following treatment may be useful in predicting relapse. There is evidence showing that the presence and size of radiographic lesions resulting from healed TB are important determinants of risk for reactivation of TB. Linh et al. assessed the reproducibility, sensitivity and specificity of various radiographic predictors of subsequent TB in a selected cohort of migrants to Australia who were followed for approximately 10 years. The presence of calcified nodular densities or fibrosis together with non-calcified nodular densities in mid and/or upper lung zones or the presence of a pulmonary infiltrate typical of TB had a sensitivity of 66% for subsequent pulmonary TB and a specificity of 82%.⁴⁵

A similar study in 326 South African mine workers showed that the presence of cavitation following successful cure from drug-susceptible TB was also a risk factor for relapse. During follow-up (median 25.1 months) 65 patients (20%) had a recurrent episode of tuberculosis, a recurrence rate of 10.3 episodes per 100 person-years at risk (PYAR): 16.0 per 100 pyar in HIV-1-positive patients and 6.4 per 100 pyar in HIV-1-negative patients. Paired DNA fingerprints were available in 39 of 65 recurrences: 25 pairs were identical (relapse) and 14 were different (reinfection). Of recurrences within the first 6 months after cure, 93% (13/14) were attributable to relapse compared with 48% (12/25) of later recurrences.⁴⁶

In USPHS Study 22 of rifapentine used in the continuation phase of drug-susceptible TB treatment, the end-of-treatment chest x-ray was evaluated as an independent risk factor for TB relapse. Relapse occurred in 17.3% of subjects with persistent cavity on chest x-ray, in 7.6% of subjects with a cavity that resolved by end-of-treatment, and 2.5% (P=0.002 for trend) of subjects who never had a cavity. In multivariable analysis, patients with persistent cavity on end-of-treatment chest x-ray were significantly more likely to relapse than patients with no cavity on baseline or 2-month chest x-ray (hazard ratio [HR]

⁴⁵ Linh NN, Marks GB, Crawford ABH. Radiographic predictors of subsequent reactivation of tuberculosis. *Int J Tuberc Lung Dis* 2007;11(10):1136-42.

⁴⁶ Sonnenberg P, Murray J, Glynn J R, et al. HIV-1 and recurrence, relapse and reinfection of tuberculosis after cure: a cohort study in South African mineworkers. *Lancet* 2001;358:1687-93.

4.22, 95% CI 2.00-8.91), and were more likely to relapse than subjects whose early cavity had resolved by the end-of-treatment chest x-ray (HR 1.92, 95% CI 1.09-3.39). The authors concluded that persistent cavity after 6 months of TB treatment was independently associated with disease relapse after controlling for other variables.⁴⁷

MDR-TB

In patients with MDR-TB, the extent of residual lung damage after completion of treatment was evaluated by chest radiograph and lung function tests at the end of treatment. The radiographs were read by two independent observers who attributed a zonal score of between 0 and 18, depending on the extent of radiographic abnormalities (opacification or cavitation), counted the number of visible cavities and measured the diameter of the largest cavity. Almost all patients were considered as having an abnormal chest radiograph. The mean zonal score was 6.5. Cavitation was present in more than half of the patients. Of 33 patients, 31 (94%) had abnormal lung function tests. The median FEV1 was 63% and FVC was 57% of the predicted value. Restrictive and combined restrictive-obstructive lung function patterns were the predominant abnormalities. The authors concluded that residual lung damage in MDR-TB patients who completed treatment is common and extensive and may increase the risk of relapse of tuberculosis and reduce the life expectancy of these patients. They also noted that the extensive residual damage may be attributed to the duration of active TB (mean 52 months).⁴⁸

Recurrence of clinical symptoms may signify relapse of the initial infection or reinfection. The longer the duration of follow-up, the less likely recurrence is to due relapse and the more likely it is due to reinfection. In the high endemic area of Cape Town, South Africa, all patients with reported TB in the area between 1993 and 1998 were followed up to 2001 for disease needing retreatment (i.e., recurrence). Patients who had MDR-TB or who had treatment failure, were transferred, or died during treatment were excluded. Analysis was restricted to patients for whom DNA fingerprinting of their TB isolates was obtained. Median duration of follow-up was 5.2 years. Recurrent TB occurred in 108 of 612 (18%) patients, of whom 61 of 447 (14%) experienced recurrence after successful treatment, and 47 of 165 (28%) experienced recurrence after default. Of the 108 patients with recurrent TB, 68 (63%) had a DNA fingerprint in the second episode. Among these patients, 24 of 31 (77%) recurrences after successful treatment and 4 of 37 (11%) recurrences after default were attributable to reinfection. The reinfection disease rate after successful treatment was estimated at 2.2 per 100 person-years. The authors concluded the age-adjusted incidence rate of TB attributable to reinfection after successful treatment was four times that of new TB.⁴⁹

Drug-Susceptible Tuberculosis in HIV-positive patients

⁴⁷ Hamilton CD, Stout JE, Goodman PC, et al. The value of end-of-treatment chest radiograph in predicting pulmonary tuberculosis relapse. *Int J Tuberc Lung Dis* 2008;12(9):1059-64.

⁴⁸ De Valliere S, Barker RD. Residual lung damage after completion of treatment for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2004;8(6):767-71.

⁴⁹ Verver S, Warren RM, Beyers N, et al. Rate of reinfection tuberculosis after successful treatment is higher than rate of new tuberculosis. *Am J Respir Crit Care Med* 2005;171(12):1430-5.

In patients with HIV infection, the patient's underlying immune function has been shown to predict relapses in patients treated for drug-susceptible TB. An undetectable viral load and increasing CD4-cell counts with antiretroviral therapy (ART) were associated with the absence of TB relapses.⁵⁰ Therefore, patients with HIV infection on ART treated for MDR-TB, should be followed clinically to assess continued efficacy and compliance with ART in order to decrease the risk of MDR-TB relapse.

5. Summary of Published Data in MDR-TB in the Presence of HIV Infection (see also Appendix B for Table of Studies)

The clinical presentation of MDR-TB in the HIV-seropositive patient is not dissimilar to that of drug-susceptible TB in the HIV-seronegative patient. However, in HIV-positive patients, the clinical presentation of TB disease may be confused with other pulmonary or systemic infections, and is more likely to be extrapulmonary or sputum-negative than in HIV-negative patients, especially if advanced HIV infection is evident.

As mentioned in Section 7 “Overview of Recommended Drugs and Treatment Regimens for Drug-Resistant TB”, the recommended treatment for drug-resistant TB is the same for HIV-positive as for non-HIV-positive patients, except for the use of thioacetazone, which is not recommended for use in HIV-seropositive patients. However, treatment is much more difficult and adverse events more common in HIV patients. Deaths during treatment, caused by TB itself or by other HIV-related diseases, are more frequent in HIV-positive patients, particularly in the advanced stages of immunodeficiency. Delays in diagnosis can lead to higher morbidity or mortality.

The use of anti-retroviral therapy (ART) in HIV-positive patients with TB improves survival and slows progression to AIDS. However, initiation of ART in HIV-positive patients with drug-susceptible or drug-resistant TB can be complicated by drug-drug interactions and adverse events that may lead to loss of efficacy or interruption of both TB and/or HIV therapy. In general, HIV patients have a higher rate of adverse drug reactions to both TB and non-TB medications.

As discussed above in Section 4.2.1 “Summary of Published Data in MDR-TB” we performed a literature search with the purpose of obtaining information on endpoints and treatment outcome separately for HIV-positive and HIV-negative patients.

See Appendix B for Table of Data on HIV-Positive Subjects from Published Trials of MDR-TB

The data HIV-positive patients (see Appendix B) was compared to the data from HIV-negative patients (see Appendix A). We attempted to determine whether the same endpoints and timing of assessment of the endpoints should be the same or different in the populations examined. **Appendix C contains the bibliography for these studies.**

⁵⁰ Lopez-Cortes FL, Marin-Niebla A, Lopez-Cortes LE, et al. Influence of treatment and immunological recovery on tuberculosis relapses in HIV-infected patients. *Int J Tuberc Lung Dis* 2005;9(12):1385-90.

The main differences that were noted between the two groups of studies are noted below:

There were significantly fewer studies on HIV-positive patients that fit the criteria for the FDA review

Location: The majority of the studies found were conducted in more industrialized countries (four in the U.S.A., one in France, and one in Germany). None were conducted in resource-limited sites or countries, which is in sharp contrast to studies on HIV-negative patients. This is an interesting point, because the burden of HIV and MDR-TB is in developing countries, but there are fewer studies that are conducted in these sites.

Type of Study: As with the studies with HIV-negative patients, most of these studies were retrospective (four), while two were prospective. The same inherent limitations noted regarding studies in HIV-negative patients applies here.

HIV status: The majority of the studies included both HIV-positive and HIV-negative patients (except for Fischl 1992, in which all 62 patients were HIV-positive). The patients were stratified by HIV status, though not for the purposes of sputum analysis, cure, or treatment completion. The table below shows the percentages of HIV-positive patients in each study:

STUDY	HIV Rate
Fischl	62 patients (100%)
Salomon	17/18 patients with MDR-TB (84%)
Narita	31/70 evaluable patients (44%)
Munsiff	512/856 patients (60%)
Uffredi	9/45 patients (20%)
Eker	7/142 patients (4.9%)

Differences in sputum conversion and other endpoints, stratified by HIV status, would have yielded important information. It appears also that studies specifically aimed at evaluating MDR-TB treatment outcomes in HIV-positive patients are lacking.

Demographics: There were no significant differences between these patients and HIV-negative patients.

Disease characteristics: As with the studies on HIV-negative patients, information was provided on chest radiography findings (Fischl 1992, Narita 2001, Munsiff 2006, Uffredi 2007, and Eker 2008), EPTB (Fischl 1992, Uffredi 2007 and Eker 2008), and surgery (Uffredi 2007).

Resistance: The resistance of isolates ranged from 1 to 5.5, similar to the pattern seen with HIV-negative patients.

Regimen: Five treatment regimens were individualized, while one (Salomon 1995) was standardized. Only Uffredi and Munsiff reported use of FQs.

Duration of Regimen: The durations were similar to those of the HIV-negative patients.

Clinical symptoms: Fischl and Salomon were the only studies that reported on clinical symptom resolution. Most patients in the Fischl study (all of whom were HIV-positive) have constitutional symptoms, with few differences between cases (resistant to ≥ 2 drugs) and controls (resistant to 1 drug, or drug-susceptible). Cases were 5 times less likely to have resolution of fever and 7 times less likely to gain 5 lbs in weight or more. The Salomon study stated that 67% (59/88 patients) of the cohort had fever at enrollment, and this finding was more frequent in the HIV-positive patients, who comprised 84% of the cohort. Fever was also more likely to persist for more than 14 days in this group of patients. Those HIV-positive patients with miliary TB were less likely to defervesce than uninfected patients.

Such clinical information on HIV-positive patients is helpful and useful in determining clinically meaningful endpoints.

Completion and Cure: Similar issues as those seen with HIV-negative patients were discovered in these studies. The definitions were, at times, unclear. Munsiff (2006) stratified completion by HIV status, showing that 17% (87/512 patients) of HIV-positive patients completed therapy, compared with 59.3% (105/177 patients) of HIV-negative patients.

Smear conversion: Both smear and culture conversion results were provided for the majority of the studies, perhaps reflecting the difficulty in diagnosing TB in HIV-positive patients due to potential differences in mycobacterial burden, depending on the extent of TB disease. Most smears converted within 1 to 2 months.

Sputum culture conversion: The time to culture conversion varied from 19 days in inpatients (Narita 2001) to 61.5 days (Eker 2008). The time to conversion did not appear to be longer than that for HIV-negative patients. The conversion rate ranged from 8% (Fischl 1992) to 74.6% (Eker 2008).

Relapse: Only 3 papers provided information on relapse. Fischl reported that 1 of 2 patients (50%) had relapse of sputum culture at 496 days after conversion. Of 227 patients in the Munsiff paper who completed therapy, 8 patients (3.5%) relapsed. This paper also stratified the results by HIV status, indicating that 5 of the 512 HIV-positive patients (1%) relapsed. None of the 11 patients in the Salomon paper had relapsed after 80 months of follow-up. The other three papers did not provide information on relapse.

Failure: There were few conclusions that could be drawn by comparing the failure rates across the studies. The Eker study showed a failure rate of 0.6% (1 of 177 patients failed therapy, while 23/25 patients in the Fischl study who received effective therapy (92%)

produced persistently positive sputum cultures. As with relapse, none of the patients in the Salomon paper failed therapy.

Follow-up: Follow-up time after treatment was completed ranged from a median of 9.7 months in the Salomon paper, to 3.7 years in the Munsiff paper. Two papers (Fischl and Narita) did not provide these data. The period of follow-up appeared to be similar in papers studying HIV-positive patients and those that assessed HIV-negative patients.

Default/Loss-to-follow-up: The default rates were not significantly different in the HIV-positive patients, as compared to the HIV-negative patients. The papers provided rates ranging from 0.6% (1 patient out of 177 in the Eker trial) to 16% in the Uffredi trial.

Mortality: This factor contrasted the most among these HIV-positive patients when compared to HIV-negative patients. Mortality rates were very high, reflecting a theme that is noted throughout the literature. The Fischl trial showed that of 32 patients who received treatment for less than 2 months, 24 of them (75%) died of TB. Even for those who received treatment for 2 or more months, 27% (8 of 30 patients) died of TB. It was also shown in this study that patients with AIDS and TB had significantly shorter survival time than asymptomatic or symptomatic co-infected patients (relative risk, 4.33; 95% confidence interval, 1.8-10.5, $p=0.001$). Twenty-six of the 81 patients in the Narita trial (32%) died, while all-cause mortality in the Uffredi trial was 27% (12 of 45 patients died), and TB-related mortality was 66.6% (8 of 12 patients died). In the Munsiff trial, 271 of the 610 patients who were treated for MDR-TB (44.4%) died prior to treatment completion. While receiving treatment, 233 of the 512 HIV-positive patients (45.4%) died.

Two other trials had lower but still significant mortality rates. Salomon showed that 5 of 57 patients (9%) died: 3 from TB disease and 2 from non-TB-related causes. Eker showed that 14 of 177 patients (7.9%) died.

Other issues: Not discussed in the papers reviewed were issues concerning treatment of both TB and HIV co-infection. None of the papers except Salomon addressed the significance of ARV treatment in relation to TB treatment, and the drug-drug interactions that can potentially occur (18 of 57 patients (32%) in this paper elected to take ARVs; this was the extent of the ARV discussion). Granted, rifamycins are usually contraindicated for use together with protease inhibitors and non-nucleoside reverse transcriptase inhibitors, and MDR-TB treatment should, theoretically, exclude the use of RIF, rifabutin, and rifapentine. There were instances, however, when patients were administered drugs to which their mycobacterial isolates were not fully susceptible, so these DDIs could be an issue in a study.

Also not discussed at any great length is the effect of CD4 count as a marker of severity of immunosuppression, and what effect that might have on treatment success and other outcomes such as sputum conversion, failure and mortality.

The data in HIV-positive patients was compared to the data from HIV-negative patients. An attempt was made to determine whether the same endpoints and timing of assessment of the endpoints should be the same or different in the populations examined.

The table below shows comparisons between HIV-negative and HIV-positive patients with respect to sputum culture conversion, median/mean time of sputum culture conversion, relapse rate, failure, and mortality (all-cause and TB-related). Many of the differences have been discussed in the narrative above.

Comparison between HIV-Uninfected and HIV-Infected Patients of Sputum Culture Conversion, Time of Sputum Culture Conversion, Relapse Rate, and Mortality (From Literature Review)

STUDY	Sputum Culture Conversion	Median Time of Sputum Culture Conversion (range)	Relapse Rate	Failure	Mortality (All-cause/TB-related)
HIV-NEGATIVE PATIENTS					
Goble	65% (87/134)	2 mos. (1-8)	14%	35%	37%/22%
Telzak	68% (17/25)	69 days (2-705)	0%	0%	No data/4%
Suo	65% (11/17)	2 mos.	0%	24%	35%/No data
Park	82.5% (52/63)	2 mos. (1-10)*	0%	18%	0%
Geerlings	79% (23/29)	6 weeks (1-20)	2.2%	21%	14%/2.2%
Yew	81% (51/63)	2.1 mos. (1-5)*	2.1%	14.3%	No data/4.7%
Kim	88.5% (431/487)	2.1 mos. (1-13)*	2.4%	8.1%	3.1%/No data
Tahaoglu	95% (150/158)	1.9 mos. (1-9)*	1.3%	8%	4%/No data
Suarez	68% (153/158)	3 mos.	0%	32.2%	11%/No data
Chan	85% (137/162)	3 mos.	8.6%	15%	25%/12%
Palermo	75.5% (105/141)	5.2 mos. (2.9-7.5)	11.9%	9.2%	19%/No data
Shean	56% (276/491)	152 days (72-136)	11%	5%	14%/No data
Holtz	77% (129/167)	60 days (4-462)	2%	1%	7.8%/No data
HIV-POSITIVE PATIENTS					
Fischl	8% (2/225)	No data	50%	92%	53.3%/27%
Salomon	89% (8/11)	2 mos.	0%	0%	9%/
Narita	No data	39 days (-33-211)	No data	2.85%	32%/No data
Munsiff	No data	No data	3.5%	28.4%	44.4%/No data
Uffredi	No data	No data	No data	14%	27%/17%
Eker	74.6% (132/177)	61.5 days	No data	0.6%	7.9%/No data

*Mean value

There was much similarity between the endpoints for HIV-negative patients and HIV-positive patients in these trials. Due to the heterogeneity of the trials themselves, as well as the small number of studies involving HIV-positive patients, it is difficult to draw many conclusions about which endpoints consistently differ between the two groups of patients.

While the range of sputum culture conversion rates was wider in the HIV-positive population compared with the HIV-negative population (7%-89% vs. 56%-95% respectively), this early endpoint was still predictive of treatment outcome, e.g. in the Fischl study, a 7% sputum culture conversion rate was associated with a 50% relapse rate, while a 89% conversion rate in the Solomon study had a 0% of relapse. Thus the same trends observed in the HIV-negative population regarding sputum culture conversion and relapse rates were seen in the HIV-positive population. Beyond such general trends however, it is difficult to comment on whether the early endpoint of sputum culture conversion performs better in one population versus the other due to the small number of studies involving HIV-positive patients as mentioned earlier. Therefore the use of sputum culture conversion as an early endpoint in the HIV and MDR-TB co-infected population requires further validation.

The most significant difference that was noted, however, was in the rates of mortality. HIV-positive patients have a much higher mortality than those who are not infected. This late endpoint is a difficult one to assess in long-term MDR-TB studies due to factors such as default/loss-to-follow-up, and the fact that a significant number of patients who receive adequate, directly observed therapy for their disease, may not end up dying. Given that the data show this increased mortality in HIV-positive patients, investigators in MDR-TB trials should attempt to account for this fact in the design of their studies.

6. Lessons Learned from Susceptible TB and HIV Infection

6.1. Rifapentine (Priftin®)

As discussed in earlier sections in this document, there is limited information regarding use of sputum conversion as an endpoint and predictor of relapse as well as the optimal timing for both endpoints in MDR-TB. Therefore, rifapentine, a drug approved for drug-susceptible TB will be used to illustrate these points.

Rifapentine (Priftin®) was approved for the treatment of pulmonary tuberculosis caused by *Mycobacterium tuberculosis* on June 22, 1998. The application was approved under the accelerated approval regulations (21 CFR 314 Subpart H): it was felt that new agents were needed in regimens that would require fewer directly observed therapy visits, potentially decreasing non-compliance thus contributing to a public health need to reduce the number of tuberculosis cases in the United States. As required in subpart H, the surrogate endpoint utilized in the NDA clinical trial (Study 008) was the relapse rate 6-months following a 6 month treatment course. In October 20, 2000 follow-up data from Study 008 to assess relapse through 24 months following the end of treatment was submitted.

Study 008: Rifapentine vs. Rifampin (initial and continuation phase treatment)

The initial rifapentine NDA submission included interim efficacy results based on data collected through November 8, 1996 from a clinical trial (Study 008) for the treatment of drug-susceptible TB. To better understand the incidence of relapse, the applicant with prior FDA agreement, submitted a clinical update on March 4, 1998 that summarized

follow-up data through a July 1997 cut-off date. By this date, all of the patients would have been treated and followed to the 6-month post therapy visit.

Study 008 was an open-label, prospective, parallel group, active controlled trial in patients with pulmonary tuberculosis, excluding those with HIV-infection.

- In the initial 2 month phase of treatment (60 days), 361 patients received rifapentine 600 mg twice a week in combination with daily isoniazid, pyrazinamide, and ethambutol and 361 subjects received rifampin 600 mg in combination with isoniazid, pyrazinamide and ethambutol all administered daily. The doses of the companion drugs were the same in both treatment arms during the initial phase: isoniazid 300 mg, pyrazinamide 2000 mg, and ethambutol 1200 mg. For patients weighing less than 50 kg, the doses of rifampin (450 mg), pyrazinamide (1500 mg) and ethambutol (800 mg) were reduced. Ethambutol was discontinued when isoniazid and rifampin susceptibility testing results were confirmed.
- During the 4 month continuation phase, 321 patients in the rifapentine group continued to receive rifapentine 600 mg dosed once weekly with isoniazid 300 mg and 307 patients in the rifampin arm received twice weekly rifampin and isoniazid 900 mg. For patients weighing less than 50 kg, the doses of rifampin (450 mg) and isoniazid (600 mg) were reduced.

Treatment was directly observed. Both treatment groups received pyridoxine (Vitamin B6) over the 6 month treatment period.

The table below presents the clinical data from the trial through 6 months of follow-up⁵¹:

Study 008: Clinical Outcome in HIV Negative Patients with Pulmonary Tuberculosis		
	Rifapentine Combination Treatment % and (n/N*)	Rifampin Combination Treatment % and (n/N*)
Status at End of Treatment (Month 6)		
Converted	87% (249/286)	81% (229/284)
Not Converted	1% (4/286)	3% (8/284)
Lost to Follow-up	12% (33/286)	17% (47/284)
Status Through 6 Month Follow-up:		
Relapsed	10% (25/249)	5% (11/229)
Sputum Negative, still being followed	81% (201/249)	90% (205/229)

⁵¹ Prifitin package insert approved June 22, 1998: [www. drugs@fda.gov](http://www.drugs@fda.gov)

Lost to Follow-up	9% (23/249)	6% (13/229)
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* All data through 8 July 1997 for patients with confirmed susceptible *M. tuberculosis* (rifapentine combination N=286; rifampin combination N=284)

Sputum conversion was assessed at the end of the intensive phase of treatment (2 months) and was similar in both groups: 75% in the rifapentine group and 79% in the rifampin treatment group (4% treatment difference (95% CI: -2.5%, 11.3%).⁵² However, as shown in the table, the risk of relapse 6 months following completion of treatment (intensive and continuation phases) was greater in the group treated with the rifapentine combination.

An analysis was performed by the FDA Statistical Reviewer to determine whether the increased relapse rate in the rifapentine arm could have been an artifact of incomplete follow-up.⁵³ The analysis showed that there was no evidence that the risk of relapse on rifapentine diminished with longer follow-up:

Study 008: TIME TO RELAPSE*
Number Relapsed

Post Treatment Period	Rifampin	Rifapentine
0-3 Months	5	10
4-7 Months	5	9
≥ 8 month	1	7

*data through July 1997 (patients followed at least 6 months following the end of treatment)

The Reviewer also examined the interaction of treatment with response by end of the intensive phase regimen (day 60). Response was stratified three ways: converted or not by day 60, two negative cultures by day 60, and positive or negative on culture at day 60. As shown in the table below, patients who did not convert at the end of the intensive phase of treatment were at a higher risk of relapse, regardless of which treatment group they were in.⁵⁴

STUDY 008	RELAPSES* Through 6 months of Follow-up		Difference Rifapentine – Rifampin (CI)	Relative Risk
	Rifampin N=229	Rifapentine N=249		
Converted by day 60	5% (172)	7% (177)	3% (-2%, 8%)	1.57
Not Converted by day 60	6% (51)	19% (67)	14% (2%, 25%)	3.30
Two negative cultures by day 60	2% (89)	7% (89)	4% (-2%, 11%)	3.00
< 2 negative cultures by day 60	7% (133)	13% (155)	6% (-1%, 13%)	1.91
Negative on day 60 culture	4% (187)	9% (193)	5% (0%, 9%)	2.06
Positive on day 60 culture	9% (35)	18% (51)	9% (-5%, 23%)	2.06

*data through July 1997 (patients followed at least 6 months following the end of treatment) – data on a few patients not available for each cell

⁵² Priftin NDA Medical Officer Review. June 22, 1998: <http://www.fda.gov/cder/foi/nda/98/21024.htm>

⁵³ Priftin NDA Statistical Review. June 22, 1998: <http://www.fda.gov/cder/foi/nda/98/21024.htm>

⁵⁴ Priftin NDA Statistical Review. June 22, 1998: <http://www.fda.gov/cder/foi/nda/98/21024.htm>

Other analyses were performed which determined that poor compliance to the companion medications (i.e., isoniazid and ethambutol) may have accounted for many of the relapses in the rifapentine group.

An Anti-Viral Advisory Committee Hearing (May 5, 1998) was held to discuss the efficacy and safety of rifapentine as demonstrated in the initial submission of Study 008 containing interim data through 6 months of follow-up after the end of treatment. The committee voted to recommend approval of rifapentine. They expressed concern about the use of rifapentine in HIV positive patients. In general, the committee believed that rifampin and rifapentine would be comparable agents; however, the optimal therapeutic regimen has not been determined for rifapentine. The committee recommended further studies, including the completion of the USPHS Study 22, which utilizes rifapentine in the last 4 months of therapy at a weekly dose with INH, and standard rifampin therapy in the first two months of intensive therapy.

When Study 008 was completed the results were submitted to the NDA on December 17, 1999 and reported through 24 months of follow-up as shown below⁵⁵:

Study 008: Clinical Outcome in HIV Negative Patients with Pulmonary Tuberculosis		
	Rifapentine Combination Treatment % and (n/N)	Rifampin Combination Treatment % and (n/N)
Status Through 24 Month Follow-up*:		
Relapsed	12% (29/248)	7% (15/226)
Sputum Negative	57% (142/248)	64% (145/226)
Lost to Follow-up	31% (77/248)	29% (66/226)

* Twenty-two (22) deaths occurred during the study; 11 in each treatment arm

An analysis correlating sputum conversion at 2 months with relapse following 24 months of follow-up, as was done with the 6 month data, was not performed by the review team.

Upon review of the final data from this study, the FDA Statistical Reviewer concluded that:

[Sputum] [c]onversion rates [at the end of 6 months of treatment] were higher for rifapentine patients, but relapse rates were also higher for rifapentine patients. If we exclude patients who were lost to follow-up, the relapse rates are 17% (29/171) for rifapentine patients and 9% (15/160) for rifampin patients (p=0.052 using Fisher's exact test; 95% confidence interval for the difference in rates; rifapentine minus rifampin, of (-0.2%, 15.4%) using the normal approximation to the binomial distribution incorporating the continuity correction). The odds ratio corresponding to this difference is 1.97, with an asymptotic, corrected 95% confidence interval of (1.00, 3.17). If we assume that patients who were lost to follow-up relapsed, the relapse rates are 43% (106/248) for rifapentine patients and 36% (81/226) for rifampin patients (p=0.13 using Fisher's exact test; 95%

⁵⁵ Adapted from Priftin package insert approved October 20, 2000: www.drugs@fda.gov

confidence interval for the difference in rates, rifapentine minus rifampin, of (-2.3%, 16.1%) using the normal approximation to the binomial distribution incorporating the continuity correction). The odds ratio corresponding to this difference is 1.34, with an asymptotic, corrected 95% confidence interval of (0.95, 1.49). Finally, if we assume that patients who were lost to follow-up did not relapse, relapse rates are 12% (29/248) for rifapentine patients and 7% (15/226) for rifampin patients ($p=0.08$ using Fisher's exact test; 95% confidence interval for the difference in rates, rifapentine minus rifampin, of (-0.5%, 10.6%) using the normal approximation to the binomial distribution incorporating the continuity correction). The odds ratio corresponding to this difference is 1.86, with an asymptotic, corrected 95% confidence interval of (0.96, 3.12).

Excluding patients who were lost to follow-up, relapse rates are approximately double on the rifapentine arm (17% versus 9%). The absolute difference and odds ratio are smaller using the two other estimation techniques discussed above as both impute the same type of response for a patient, regardless of which treatment they received. Generally, relapse rates appear to be higher on the rifapentine arm. There is a substantial amount of missing data, however, which weakens any conclusions that can be drawn from this study. Approximately a third of all patients who converted were lost to follow-up.⁵⁶

USPHS Study 22: Rifapentine vs. Rifampin (continuation phase treatment)

A second trial of rifapentine as a component of the continuation phase was conducted by the CDC (Study USPHS 22). This was a randomized, open-label trial in 1075 HIV seronegative and seropositive patients with pulmonary tuberculosis. Patients with culture-positive, drug-susceptible pulmonary tuberculosis who had completed the initial 2 month phase of treatment with 4 drugs (rifampin, isoniazid, pyrazinamide, and either ethambutol or streptomycin) under direct observation were randomly assigned to receive either rifapentine 600 mg and isoniazid 15mg/kg (max 900 mg) once weekly or rifampin 10 mg/kg (max 600 mg) and isoniazid 15 mg/kg (max 900 mg) twice weekly for the 4 month continuation phase. Study drugs were given under direct observation therapy in both arms.

In the rifapentine arm, 502 HIV seronegative and 36 HIV seropositive patients were randomized and in the rifampin arm 502 HIV seronegative and 35 HIV seropositive patients were randomized to treatment. Enrollment of HIV seropositive patients was stopped when 4 of 36 patients in the rifapentine combination group developed rifampin monoresistance.

Pre-randomization there were approximately 68% and 73% of patients who were ultimately randomized to rifapentine and rifampin, respectively, had converted by 2 months (baseline). 12% had missing culture data at baseline.

The table below contains assessments of sputum conversion at the end of treatment (6 months total: 2 months of initial and 4 months of randomized continuation treatment) and relapse rates at the end of follow-up (24 months) in all HIV seronegative patients randomized to treatment.

⁵⁶ Priftin NDA Statistical Review. October 20, 2000
http://www.fda.gov/cder/foi/nda/2000/21024S5_Priftin.htm

The failure and relapse rates reported in this study could be underestimated due to the limitation of the microbiologic methods used in the study. Positive culture was based on either one sputum sample with >10 colonies on solid media OR at least 2 positive sputum samples on liquid or solid media. However, only one sputum sample was collected at each visit in a majority of patients.

USPHS Study 22: Clinical Outcome in HIV Negative Patients with Pulmonary Tuberculosis		
	Rifapentine Combination Treatment % (n/N)	Rifampin Combination Treatment % (n/N)
Status at End of 4 Months Continuation Phase		
Treatment Response *	93.8% (471/502)	91.0% (457/502)
Not Converted	1.0% (5/502)	1.2% (6/502)
Did Not Complete Treatment**	4.2% (21/502)	7.0% (35/502)
Deaths	1.0 % (5/502)	0.8% (4/502)
Status Through 24 Month Follow-up:		
Relapsed	8.7% (41/471)	4.8% (22/457)
Sputum Negative	79.4% (374/471)	80.1% (366/457)
Lost to Follow-up	7.9% (37/471)	9.8% (45/457)
Deaths	4.0% (19/471)	5.3% (24/457)

* Treatment response was defined as subjects who responded successfully after 16 doses of rifampin and isoniazid or after 8 doses of rifapentine and isoniazid, and remained sputum negative through the end of continuation phase therapy.

**Due to drug toxic effects, non-adherence, withdrawal of consent, receipt of nonstudy regimen, other.

As shown in the table, at the end of the 4 month continuation phase (6 months of treatment total) treatment response rates in HIV seronegative patients were similar between the rifapentine (94%) and rifampin (91%) groups, however, relapse rates through 24 months of follow-up were numerically higher in the rifapentine group (9% vs. 5%, respectively). Loss to follow-up in Study 22 (< 10%) was much less than in Study 008 (approximately 30%).

Higher relapse rates in HIV seronegative patients were seen in patients with a positive sputum culture at 2 months (i.e., at the time of study randomization), cavitation on chest x-ray, and bilateral pulmonary involvement.

Seventy-one HIV seropositive patients were enrolled into the study. There were no treatment failures during the on-treatment phase of the study. Sixty-one patients completed therapy and were assessed for relapse. The rates of relapse were 16.7% (5/30) in the rifapentine group and 9.7% (3/31) in the rifampin group.

Risk factors that predisposed to relapse in the HIV seropositive patients included the presence of both pulmonary and extrapulmonary disease at baseline, low CD4 counts, use of azole antifungals and younger age.

In HIV seropositive patients, 4 of the 5 relapses from the rifapentine combination group involved *M. tuberculosis* strains with rifampin monoresistance. No relapse strain in the twice weekly rifampin/isoniazid group had acquired drug resistance. These findings are consistent with other cases of acquired rifampin monoresistance in HIV seropositive adults who failed or relapsed after treatment with intermittent regimens with isoniazid and other rifamycins (rifampin and rifabutin).

The death rate among all study participants did not differ between the rifapentine and rifampin treatment groups.

An analysis was conducted to evaluate sputum conversion rates at 2 months in HIV negative patients in Study 22 (which occurred prior to study randomization) independent of the intensive phase regimen and the correlation with relapse during the 24 months of follow-up. The following table shows the cross-tabulation of culture results at pre-randomization (2 months) and final outcome results for all of study 22.

Table: Pooled treatment arms: Overall outcome by sputum culture conversion

24 month results	Sputum Negative N = 740	Not converted/ Relapse N =74	Death N = 52	Did not complete Trt/ Loss to follow-up N = 138
2 month sputum conversion				
Yes	553	33	34	86
No	110	37	8	25
Other/missing	77	4	10	27

There are missing data for both 2 month conversion status as well as at for the 24 month results. If all missing data are excluded for subjects with 2 month conversion, the probability of cure is 553/620 (89%) (Positive Predictive Value) (95% CI [87, 92]), as opposed to 110/155 (71%; (95% CI [64, 78]) for those without 2 month conversion. The results are similar within each treatment arm. In the Rifapentine arm for subjects with 2 month conversion, the probability of cure is 88% (PPV), as opposed to 70% for those without conversion. In the Rifampin arm for subject with 2 month conversion, the probability of cure is 90% (PPV), as opposed to 72% for those without conversion.

If missing 24 month data are considered as negative events, the probability of cure is 553/706 (78%) (PPV) (95% CI [75, 81]), as opposed to 110/180 (61%; 95% CI [54, 68]) for those without conversion. In the Rifapentine arm for subjects with 2 month conversion, the probability of cure is 78% (PPV), as opposed to 62% for those without conversion. In the Rifampin arm for subjects with 2 month conversion, the probability of cure is 78% (PPV), as opposed to 60% for those without conversion. Lastly, if missing 2 year data are considered as positive events, the probability of cure is 639/706 (91%)

(PPV) (95% CI [88, 93]), as opposed to 135/180 (75%) (95% CI [69, 81]) for those without conversion. In the Rifapentine arm for subjects with 2 month conversion, the probability of cure is 90% (PPV), as opposed to 74% for those without conversion. In the Rifampin arm for subject with 2 month conversion, the probability of cure is 91% (PPV), as opposed to 77% for those without conversion. Again there is very little difference in PPV by treatment arm for any of these analyses.

The negative predictive values (probability of poor 24 month outcome given sputum positivity at 2 months) range from 25% to 40%.

Summary of Rifapentine Study Findings:

Study 008: Rifapentine vs. Rifampin (initial and continuation phase treatment)

- Rates of sputum conversion at the end of the intensive phase (2 months) were similar between the rifapentine (172/286) and rifampin (177/283) combination treatment groups.
- At the end of 6 months of treatment, conversion rates were higher for rifapentine (87%) vs. rifampin (81%) patients; however, the risk of relapse at 6 months of follow up (10% vs. 5%) and 24 months of follow-up (12% vs. 7%) was higher in the rifapentine group compared to the rifampin group.
- The higher relapse rate in the rifapentine arm may possibly be due to various factors: less frequent dosing of rifapentine, lower efficacy of rifapentine, or lower compliance with the companion drugs in the rifapentine group, differences in host factors (e.g., patients with cavitory disease).
- Lack of sputum conversion at 2 months in Study 008 was correlated with a higher rate of relapse following 6 months of follow-up in both the rifapentine and rifampin treatment groups; however, the relapse rate in the rifapentine group is higher than in the rifampin group. A similar analysis correlation conversion at 2 months with relapse following 24 months of follow-up was not performed by the review team.
- While follow-up at 6 months included data on the majority of patients (>90%), the follow up at 24 months for Study 008 accounts for approximately 70% of patients. The missing data on 30% of patients weakens any conclusions regarding relapse that could be drawn from this study.

USPHS Study 22: Rifapentine vs. Rifampin (continuation phase treatment):

- Pre-randomization there were 68% and 73% of patients who were ultimately randomized to rifapentine and rifampin, respectively, who had converted by 2 months (randomization).
- At the end of the 4 month continuation phase (6 months of treatment total) the sputum conversion rates were similar between rifapentine (93.8%) and rifampin (91%) for HIV negative patients.
- Relapse rates through 24 months of follow-up were numerically higher for HIV negative patients treated with rifapentine (8.7% vs. 4.8%) and HIV positive patients treated with rifapentine (16.7% vs. 9.7%). In both treatment groups, HIV positive patients had a higher relapse rate than HIV negative patients.

- In HIV seropositive patients, 4 of the 5 relapses in the rifapentine combination group involved *M. tuberculosis* strains with rifampin monoresistance. No relapse strain in the twice weekly rifampin/isoniazid group acquired drug resistance.
- Loss to follow-up by 24 months was lower in this study (less than 10% in both groups) than in Study 008.
- The positive predictive value of 2 month sputum culture conversion on predicting overall study results (not converted, relapse, death) varies from 78% to 91% depending on how missing data by 24 months is handled. The negative predictive value ranged from 25% to 40%.

6.2. Antiretroviral Drug Approvals for the Treatment of HIV Infection and Surrogate Endpoints

As with TB, HIV disease is treated with a combination of drugs. Consequently, experience in HIV drug development may help to inform the approach to MDR-TB drug development. Typically, patients with resistant virus who are failing current therapy are selected for study, both because the need is greatest and because there exists a potential for demonstrating efficacy, were the drug to ultimately prove efficacious. In randomized trials, the superiority of experimental drug added to optimized background therapy (OBR) over OBR plus placebo have served as the basis for the approval of new antiretroviral agents.⁵⁷

As discussed later in Section 8.4 “Choice of Comparator” it is anticipated that trials of MDR-TB will use a background regimen that has been optimized for each patient based on susceptibility test results for the individual patient’s infecting strain of mycobacteria. Initially optimized background regimens (OBR) should be based on epidemiologic information on susceptibility and then be modified when results from susceptibility testing are available; in general, patients should be on 3 to 4 drugs to which there is *in vitro* susceptibility

The selection and validation of surrogate endpoints used to evaluate and demonstrate efficacy of antiretrovirals (ARV) and serve as the basis for approval of these drugs followed a systematic approach over time. Initial approvals for ARVs (e.g., Retrovir®, zidovudine or AZT in 1987) were traditional approvals based trials with clinical endpoints (e.g., death, HIV-related illness, or AIDS-defining event). Such trials are no longer feasible or ethical to perform.

On October 30, 1991 zalcitabine (Hivid®, ddC), was submitted to FDA for NDA review in 1991 and approved 8 months later on June 19, 1992, following a recommendation from the FDA Anti-Viral Drugs Advisory Committee that the drug be approved under 21 CFR 314.500, subpart H, Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses. See Section 8.8 on “Accelerated Approval (Subpart H) Considerations.” The surrogate endpoint that supported approval was change in CD4 count.

⁵⁷ Sacks L, Behrman R. Developing new drugs for the treatment of drug-resistant tuberculosis: a regulatory perspective. *Tuberculosis* (Edinb) 2008 Aug;88 Suppl 1:S93-100.

The acceptance of CD4 as a surrogate of clinical efficacy began with a hypothesis about HIV pathogenesis and ended with an establishment of its applicability in antiretroviral clinical trials. A considerable amount of work went into validating CD4 as a surrogate endpoint and involved significant collaboration among 55 individuals in the HIV Surrogate Marker Collaborative Group. The effort included basic and clinical studies of pathogenesis, discovery of markers of disease progression, collection of data from both preclinical and clinical studies, mechanistic or semi mechanistic models, collaboration and sharing of information.⁵⁸

More recently, plasma HIV RNA was validated as a surrogate endpoint likely to predict a decrease risk for AIDS progression and death at 24 weeks on treatment based on examination of the correlation between HIV RNA and various clinical endpoints. Data collected from antiretroviral efficacy trials were analyzed to explore relationships between clinical progression of disease and the magnitude, nadir and duration of HIV RNA reductions. Five separate analyses of more than 5000 patients were performed; these analyses examined a broad range of baseline characteristics including: pretreatment CD4 T lymphocyte counts and RNA levels, prior drug experience, and treatment regimens. In the analysis a clear association between initial decreases in plasma HIV RNA within the first 24 weeks and a reduction in the risk of disease progression and death was demonstrated.⁵⁹ HIV RNA was also found to be a suitable endpoint for traditional approval if assessed at 48 weeks. Tipranavir, darunavir, enfuvirtide, maraviroc and raltegravir were approved for resistant HIV infection based on superior suppression of viral load after 24 or 48 weeks compared to background therapy (with or without a placebo or protease inhibitor).

The HIV analogy may be limited by a number of relevant differences between the management of patients with HIV infection and the treatment of TB. The first difference is that cure is not a feasible endpoint for HIV whereas it is the treatment goal in tuberculosis. Thus, while suppression of viremia is an acceptable surrogate endpoint for HIV because it has been shown to correlate with clinical prognosis, a corresponding surrogate endpoint for TB has not been established. A second issue is whether sputum conversion is a clinically-meaningful endpoint by itself, given that despite sputum conversion following treatment of initial TB infection, reactivation of disease in latent sites has sometimes been documented to occur decades after initial infection in non-HIV infected patients.⁶⁰ Additionally, although initial experience indicates that treatment outcomes in the HIV positive patients with drug susceptible TB is not different than in the HIV negative patients, an issue with MDR-TB is whether sputum conversion in MDR-TB is a valuable intermediate endpoint likely to predict and to correlate with long term cure (absence of relapse off therapy). So while a correlation has been demonstrated between HIV RNA and clinical progression of disease based on analyses of multiple

⁵⁸ Blaschke TF. Surrogate marker development: http://www.bapkpdp.org/Blaschke_BAPKPD.pdf

⁵⁹ Murray JS, Elashoff MR, Iacono-Connors, et al. The use of plasma HIV RNA as a study endpoint in efficacy trials of antiretroviral drugs. *AIDS* 1999;13:797-804.

⁶⁰ Mathena B, Kuperina NE, Bifani PJ, Kresiwirth BN. Molecular epidemiology of tuberculosis: current insights. *Clin Microbiol Rev.* 2006. 19(4):658-85.

prospective, randomized comparative clinical trials involving over 5000 patients with HIV infection, such a correlation has not been demonstrated in patients with MDR-TB. Finally, the analogy is further limited because in patients with HIV infection, clinical studies may involve the addition of one or two active agents so that patients are receiving at least two active agents as part of their treatment regimen, whereas in studies of tuberculosis, patients should be receiving at least 3 or 4 active agents as part of their regimen, per guidelines (see Section 7.2 Treatment Recommendations for Drug-Resistant TB)

7. Overview of Recommended Drugs and Treatment Regimens for Drug-Resistant TB

Treatment of drug-resistant tuberculosis (DR-TB) requires a combination various of anti-TB drugs with different mechanisms of action. Drugs to treat TB are often referred to as first- and second-line drugs (see Section 7.1 “Published Guidelines on Drugs for Treating TB”) below. Treatment guidelines using these drugs are published by the WHO (Guidelines for the Programmatic Management of Drug-resistant Tuberculosis, Emergency Update 2008) for use globally.⁶¹ The American Thoracic Society (ATS), CDC, and more recently the Infectious Disease Society of America (IDSA) also collaborate to develop joint guidelines (Guidelines for the Treatment of Tuberculosis) for the diagnosis, treatment, prevention, and control of tuberculosis in the United States.⁶²

As discussed later in this document (see Section 8 “Clinical Trial Considerations for MDR-TB), it is anticipated that clinical trials of DR-TB will use as a comparator arm consisting of a background regimen that has been optimized based on drug susceptibility test (DST) and should represent standard of care and follow treatment guidelines.

Therefore, this section will summarize the recommended anti-TB drugs and treatment regimens, principles for use in selecting a treatment regimen, duration of treatment, role of DST, considerations in treating patients with HIV co-infection, and treatment failure.

7.1. Published Guidelines on Drugs for Treating TB

The classes of anti-TB drugs have traditionally been divided into first- and second-line drugs, with isoniazid, rifampin/rifampicin, pyrazinamide, ethambutol and streptomycin being the primary first-line drugs. Examples of second-line drugs include the injectable aminoglycosides, fluoroquinolones, ethionamide, cycloserine, and PAS.

⁶¹ World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency Update 2008:

http://www.who.int/tb/publications/2008/programmatic_guidelines_for_mdrtb/en/index.html

⁶² American Thoracic Society, CDC, and Infectious Diseases Society of America. Treatment of Tuberculosis. MMWR. June 20, 2003;52(RR11);1-77.

WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis, 2008

The 2008 WHO guidelines often refer to the first-line/second-line classification but also use a group system based on efficacy, experience of use and drug class as shown:⁶³

Group 1: First-line oral drugs

isoniazid (INH), rifampin/rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB), rifabutin (Rfb)*

* Rifabutin is not on the WHO List of Essential Medicines, but it is used routinely in patients on protease inhibitors in many settings.

Group 2: Injectable agents

Streptomycin (SM); kanamycin (Km); amikacin (Am), capreomycin (Cm)

Group 3: Fluoroquinolones

ofloxacin (Ofx); levofloxacin (Lfx); moxifloxacin (Mfx)

Group 4: Oral bacteriostatic second-line anti-TB agents

Ethionamide (Eto), protionamide (Pto); cycloserine (Cs); terizidone (Trd); p-aminosalicylic acid (PAS),

Group 5: Agents with unclear efficacy (not recommended for routine use)

Clofazamine (Cfz); amoxicillin/clavulanate (Amx/Clv); clarithromycin (Clr); linezolid (Lzd); thioacetazone (Thz); imipenem/cilastatin (Imp/Cln); high dose isoniazid (16-20 mg/kg/day)

** Thioacetazone should be used only in patients documented to be HIV-negative and should usually not be chosen over other drugs listed in Group 4.

Guidelines for the Treatment of Tuberculosis: American Thoracic Society, CDC, and Infectious Diseases Society of America, 2003.

The ATS/CDC/IDSA 2003 guidelines define first line drugs as: INH, RIF, EMB, PZA.⁶⁴ Streptomycin may also be used in initial treatment; however, resistance has limited its usefulness. In addition, the other rifamycin drugs (rifabutin and rifapentine) are also considered first line drugs in special situations. Rifabutin is recommended as a substitute for RIF for patients who are receiving other drugs (e.g., anti-retrovirals) that interact with rifampin. Rifapentine is recommended be used once weekly with INH in the continuation phase of treatment for HIV-seronegative patients with noncavitary, drug-susceptible pulmonary tuberculosis who have negative sputum smears at completion of the initial phase of treatment.

⁶³ World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency Update 2008. Document no. WHO/HTM/TB/2006.402. Geneva: WHO, 2008: http://www.who.int/tb/publications/global_report/2008/en/

⁶⁴ American Thoracic Society, CDC, and Infectious Diseases Society of America. Treatment of Tuberculosis. MMWR. June 20, 2003;52(RR11);1-77

Second-line drugs, as defined by the ATS/CDC/IDSA include Cs, Eto, SM, Am, Km, Cm, PAS, and fluoroquinolones (preferred oral agent is Lfx).

7.1.1. FDA-approved Drugs for the Treatment of Tuberculosis

Not all of the WHO or ATS/CDC/IDSA recommended anti-TB drugs are FDA-approved for the treatment of TB. The 5 drugs approved for the treatment of susceptible TB are H, R, E, Z, and rifapentine. Rifabutin is approved for use in preventing *Mycobacterium avium* complex disease in patients with HIV infection but not approved for treatment of TB.

There are two fixed-dose combination preparations approved by the FDA: Rifamate® which is a combination of INH and RIF and Rifater® which is a combination of INH, RIF, and PZA.

The 5 FDA-approved drugs for second-line treatment (due to intolerance or ineffectiveness of first-line drugs) or treatment of drug-resistant organisms are S, Cm, Eto, Cs, and PAS. PAS is no longer marketed. The fluoroquinolones, Am, and Km are not approved for the treatment of TB. The following is an excerpt of the Indications and Usage section of the package insert for the 4 approved, marketed drugs.⁶⁵

Streptomycin

Mycobacterium tuberculosis: The Advisory Council for the Elimination of Tuberculosis, the American Thoracic Society, and the Center for Disease Control recommend that either streptomycin or ethambutol be added as a fourth drug in a regimen containing isoniazid (INH), rifampin and pyrazinamide for initial treatment of tuberculosis unless the likelihood of INH or rifampin resistance is very low. The need for a fourth drug should be reassessed when the results of susceptibility testing are known. In the past when the national rate of primary drug resistance to isoniazid was known to be less than 4% and was either stable or declining, therapy with two and three drug regimens was considered adequate. If community rates of INH resistance are currently less than 4%, an initial treatment regimen with less than four drugs may be considered.

Streptomycin is also indicated for therapy of tuberculosis when one or more of the above drugs is contraindicated because of toxicity or intolerance. The management of tuberculosis has become more complex as a consequence of increasing rates of drug resistance and concomitant HIV infection. Additional consultation from experts in the treatment of tuberculosis may be desirable in those settings.

Capreomycin (Capastat®)

Capastat Sulfate, which is to be used concomitantly with other appropriate antituberculosis agents, is indicated in pulmonary infections caused by capreomycin-susceptible strains of *M. tuberculosis* when the primary agents (isoniazid, rifampin, ethambutol, aminosalicylic acid, and streptomycin) have been ineffective or cannot be used because of toxicity or the presence of resistant tubercle bacilli.

Susceptibility studies should be performed to determine the presence of a capreomycin-susceptible strain of *M. tuberculosis*.

⁶⁵ www.fda.gov: drugs@fda

Ethionamide (Trecator®)

Trecator is primarily indicated for the treatment of active tuberculosis in patients with *M. tuberculosis* resistant to isoniazid or rifampin, or when there is intolerance on the part of the patient to other drugs. Its use alone in the treatment of tuberculosis results in the rapid development of resistance. It is essential, therefore, to give a suitable companion drug or drugs, the choice being based on the results of susceptibility tests. If the susceptibility tests indicate that the patient's organism is resistant to one of the first-line antituberculosis drugs (i.e., isoniazid or rifampin) yet susceptible to ethionamide, ethionamide should be accompanied by at least one drug to which the *M. tuberculosis* isolate is known to be susceptible. 3 If the tuberculosis is resistant to both isoniazid and rifampin, yet susceptible to ethionamide, ethionamide should be accompanied by at least two other drugs to which the *M. tuberculosis* isolate is known to be susceptible.

Patient nonadherence to prescribed treatment can result in treatment failure and in the development of drug-resistant tuberculosis, which can be life-threatening and lead to other serious health risks. It is, therefore, essential that patients adhere to the drug regimen for the full duration of treatment. Directly observed therapy is recommended for all patients receiving treatment for tuberculosis. Patients in whom drug-resistant *M. tuberculosis* organisms are isolated should be managed in consultation with an expert in the treatment of drug-resistant tuberculosis.

Cycloserine (Seromycin®)

Seromycin is indicated in the treatment of active pulmonary and extrapulmonary tuberculosis (including renal disease) when the causative organisms are susceptible to this drug and when treatment with the primary medications (streptomycin, isoniazid, rifampin, and ethambutol) has proved inadequate. Like all antituberculosis drugs, Seromycin should be administered in conjunction with other effective chemotherapy and not as the sole therapeutic agent.

7.2. Treatment Recommendations For Drug-Resistant TB

Randomized, comparative studies evaluating treatment in patients with various patterns of drug resistance have not been performed. Therefore, in the absence of such evidence, published treatment guidelines are derived from general principles, extrapolations and expert opinion on the management of patients with DR-TB.

Guidelines for the Treatment of Tuberculosis: American Thoracic Society, CDC, and Infectious Diseases Society of America, 2003.

The ATS/CDC/IDSA recommendations for treatment regimens in the management of drug-resistant pulmonary TB, based upon the pattern of drug resistance, is shown in the table below.⁶⁶ As noted in the table, it is recommended that patients with MDR (i.e., resistance to INH and RIF) should be treated for 18-24 months with a fluoroquinolone, PZA, EMA, an injectable agent (defined as an aminoglycoside or capreomycin), with or without an alternative agent (defined as Eto, Cs, PAS, clarithromycin, amoxicillin-clavulanate, or linezolid).

⁶⁶ American Thoracic Society, CDC, and Infectious Diseases Society of America. Treatment of Tuberculosis. MMWR. June 20, 2003;52(RR11);1-77.

Pattern of Drug Resistance	Suggested Regimen (Daily Unless Otherwise Stated)	Duration of Treatment (months)	Comments
INH (\pm SM)	RIF, PZA, EMB (a FQN may strengthen the regimen for patients with extensive disease)	6	In BMRC trials, 6 mo regimens have yielded $\geq 95\%$ success rates despite resistance to INH if four drugs were used in the initial phase and RIF plus EMB or SM was used throughout.* Additional studies suggested that results were best if PZA was also used throughout the 6 mo.** FQNs were not employed in BMRC studies, but may strengthen the regimen for patients with more extensive disease. INH should be stopped in cases of INH resistance
INH, RIF (\pm SM)	FQN, PZA, EMB, IA (\pm alternative agent)	18-24	In such cases, extended treatment is needed to lessen the risk of relapse. In cases with extensive disease, the use of an additional agent (alternative agents) may be prudent to lessen the risk of failure and additional acquired drug resistance. Resectional surgery may be appropriate.
INH, RIF (\pm SM) and EMB or PZA	FQN, (EMB or PZA if active), IA, and two alternative agents	24	Use of the first-line agents to which there is susceptibility. Add two or more alternative agents in case of extensive disease. Surgery should be considered.
RIF	INH, EMB, FQN, supplemented with PZA for the first 2 mo (an IA may be included for the first 2-3 mo for patients with extensive disease)	12-18	Daily and three times weekly regimens of INH, PZA, and SM given for 9 mo were effective in a BMRC trial,*** However, extended use of an injectable agent may not be feasible. It is not known if EMB would be as effective as SM in these regimens. An all-oral regimen for 12-18 mo should be effective. But for more extensive disease and/or to shorten duration (e.g., to 12 mo), an injectable agent may be added in the initial 2 mo of therapy.

Definition of abbreviations: BMRC = British Medical Research Council; IA = injectable agent – may include aminoglycosides (streptomycin, amikacin, or kanamycin) or the polypeptide capreomycin; FQN = fluoroquinolone – most experience involves ofloxacin, levofloxacin or ciprofloxacin; Alternative agents = Ethionamide, cycloserine, p-aminosalicylic acid, clarithromycin, amoxicillin-clavulanate, linezolid.

* Mitchison DA, Nunn AJ. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. *Am Rev Respir Dis* 1986;133:423-430.

**Hong Kong Chest Service, British Medical Research Council. Five-year follow-up of a controlled trial of five 6 month regimens of chemotherapy for tuberculosis. *Am Rev Respir Dis* 1987;136:1339-42.

*** Hong Kong Chest Service, British Medical Research Council. Controlled trial of 6-month and 9-month regimens of daily and intermittent streptomycin plus isoniazid plus pyrazinamide for pulmonary tuberculosis in Hong Kong. *Am Rev Respir Dis* 1977;115:727-35.

As mentioned in the table, surgery is recommended in some situations. However, the role of resectional surgery in the management of patients with extensive pulmonary MDR-TB tuberculosis has not been established in randomized studies. The ATS/CDC/IDSA guidelines state:

In one series, patients with severe drug resistance (on average, having resistance to more than 5 drugs) appeared to benefit from the resection of cavitory or badly damaged lung tissue when compared with historical controls. In contrast, other clinicians have reported patients with drug resistance having similar cure rates without surgery. The disparity in these reports may be due to long-standing disease with extensive fibrosis in the former group. If surgery is to be done, it

should be performed by an experienced surgeon after the patient has received several months of intensive chemotherapy. Even with successful resection, 12 - 24 additional months of chemotherapy, using drugs to which there is demonstrated susceptibility, should be given.

For areas of the world without the capacity for in vitro susceptibility testing and access to the full array of available medications, the WHO and International Union against Tuberculosis and Lung Disease (IUATLD) have formulated the principles listed below. These principles are not appropriate for industrialized nations with more ample resources, where drug-susceptibility testing (DST) should be employed in treatment decision-making.⁶⁷

- A single new drug should never be added to a failing regimen.
- When initiating or revising therapy, always attempt to employ at least three previously unused drugs to which there is in vitro susceptibility. One of these should be an injectable agent.
- Do not limit the regimen to three agents if other previously unused drugs that are likely to be active are available. In patients with MDR organisms in whom there is resistance to first-line agents in addition to INH and RIF, regimens employing four to six medications appear to be associated with better results.
- Patients should receive either hospital-based or domiciliary DOT. The implications of treatment failure and further acquired resistance are such that these cases should receive highest priority for DOT.
- Intermittent therapy should not be used in treating tuberculosis caused by drug-resistant organisms, except perhaps for injectable agents after an initial period (usually 2-3 months) of daily therapy.
- The use of drugs to which there is demonstrated in vitro resistance is not encouraged because there is little or no efficacy of these drugs (assuming the test results are accurate), and usually, alternative medications are available. However, the clinical significance and effectiveness of the use of INH in the setting of low-level INH resistance is unclear. It should be noted that the use of INH was associated with better survival rates in patients with the strain-W variety of MDR M. tuberculosis that was susceptible to higher concentrations of INH.
- Resistance to RIF is associated in nearly all instances with cross-resistance to rifabutin and rifapentine. Rare strains with RIF resistance retain susceptibility to rifabutin; this is associated with uncommon mutations of the RNA-polymerase locus in the bacillus. However, unless in vitro susceptibility to rifabutin is demonstrated, this agent should not be employed in cases with RIF resistance. Cross-resistance between RIF and rifapentine appears almost universal.
- There is no cross-resistance between SM and the other injectable agents: amikacin, kanamycin, and capreomycin (although resistance to all may occur as independent events); however, cross-resistance between amikacin and kanamycin is universal. Simultaneous use of two injectable agents is not recommended due to the absence of proof of efficacy and potential amplification of drug toxicity.
- Determination of resistance to PZA is technically problematic and, thus, is not made in many laboratories. However, resistance to PZA is uncommon in the absence of resistance to other first-line drugs. If monoresistance to PZA is observed, consideration must be given to the possibility that the etiologic agent is *M. bovis*, not *M. tuberculosis* (*M. bovis* is genotypically resistant to PZA and is not distinguished from *M. tuberculosis* by nucleic acid hybridization--probe assays that are commonly used for identification).

WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis, 2008

⁶⁷ American Thoracic Society, CDC, and Infectious Diseases Society of America. Treatment of Tuberculosis. MMWR. June 20, 2003;52(RR11);1-77.

The WHO guidelines were updated in 2008 to provide recommendations on how to manage drug-resistant TB (DR-TB) based on an assessment of the available evidence by a group of experts. Detailed strategies are described for the diagnosis of resistant strains of TB and the management of regimens designed to treat Category IV patients, defined as suspected or confirmed MDR-TB cases.⁶⁸

Treatment regimens can be standardized, empirical or individualized, as defined by the WHO:

- **Standardized treatment:** DRS [drug resistance surveillance] data from representative patient populations are used to base regimen design in the absence of individual DST. All patients in a defined group or category receive the same regimen. Suspected MDR-TB should be confirmed by DST whenever possible.
- **Empirical treatment:** Each regimen is individually designed based on the patient's previous history of antituberculosis treatment and with consideration of DRS data from the representative patient population. Commonly, an empirical regimen is adjusted when DST results on the individual patient become available.
- **Individualized treatment:** Each regimen is designed based on the patient's previous history of antituberculosis treatment and individual DST results.

Individualized treatment can also be referred to as “optimized background regimens” (OBR). Individualized treatment requires a high degree of laboratory capacity in order to perform DST of second-line drugs.

Combinations of these treatment strategies are often used as shown below:

Standardized Treatment	Representative DRS data in well-defined patient populations are used to design the regimen. All patients in a patient group or category receive the same regimen.
Standardized Treatment Followed by Individualized Treatment	Initially, all patients in a certain group receive the same regimen based on DST survey data from representative populations. The regimen is adjusted when DST results become available (often DST is only done to a limited number of drugs).
Empirical Treatment Followed by Individualized Treatment	Each regimen is individually designed on the basis of patient history and then adjusted when DST results become available (often the DST is done of both first- and second-line drugs)

As with the ATS/CDC/ISDA guidelines, the WHO recommends basic principles to consider in designing any regimen to treat DR-TB:

- Regimens should be based on the history of drugs taken by the patient.

⁶⁸ World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency Update 2008. Document no. WHO/HTM/TB/2006.402. Geneva: WHO, 2008: http://www.who.int/tb/publications/global_report/2008/en/

- Drugs commonly used in the country and prevalence of resistance to first-line and second-line drugs should be taken into consideration when designing a regimen.
- Regimens should consist of at least four drugs with either certain, or almost certain, effectiveness. If the evidence about the effectiveness of a certain drug is unclear, the drug can be part of the regimen but it should not be depended upon for success. Often, more than four drugs may be started if the susceptibility pattern is unknown, effectiveness is questionable for an agent(s) or if extensive, bilateral pulmonary disease is present.
- When possible, pyrazinamide, ethambutol and fluoroquinolones should be given once per day as the high peaks attained in once-a-day dosing may be more efficacious. Once-a-day dosing is permitted for other second-line drugs depending on patient tolerance, however ethionamide/prothionamide, cycloserine and PAS have traditionally been given in split doses during the day to reduce adverse effects.
- The drug dosage should be determined by body weight.
- Treatment of adverse drug effects should be immediate and adequate in order to minimize the risk of treatment interruptions and prevent increased morbidity and mortality due to serious adverse effects.
- An injectable agent (an aminoglycoside or capreomycin) is used for a minimum of six months and at least four months past culture conversion.
- The minimum length of treatment is 18 months after culture conversion
- Each dose is given as directly observed therapy (DOT) throughout the treatment. A treatment card is marked for each observed dose.
- DST of drugs with high reproducibility and reliability (and from a dependable laboratory) should be used to guide therapy. It should be noted that the reliability and clinical value of DST of some first-line and most of the second-line antituberculosis drugs have not been determined. DST does not predict with 100% certainty the effectiveness or ineffectiveness of a drug. DST of drugs such as ethambutol, streptomycin and Group 4 and 5 drugs does not have high reproducibility and reliability; these guidelines strongly caution against basing individual regimens on DST of these drugs.
- Pyrazinamide can be used for the entire treatment if it is judged to be effective. Many DR-TB patients have chronically inflamed lungs, which theoretically produce the acidic environment in which pyrazinamide is active. Alternatively, in patients doing well, pyrazinamide can be stopped with the injectable phase if the patient can continue with at least three certain, or almost certain, effective drugs.
- Early DR-TB detection and prompt initiation of treatment are important factors in determining successful outcomes.

The table below describes the WHO's recommended steps for building a regimen for DR-TB treatment:

STEP 1	Use any available Group 1: First-line oral agents pyrazinamide ethambutol	Begin with any first-line agents that have certain, or almost certain, efficacy. If a first-line agent has a high likelihood of resistance, do not use it. (For example, most Category IV regimens used in treatment failures of Category II do not include ethambutol because it is likely to be resistant based on treatment history.)
STEP 2	Plus one of these Group 2: Injectable agents kanamycin (or amikacin) capreomycin streptomycin	Add an injectable agent based on DST and treatment history. Avoid streptomycin, even if DST suggests susceptibility, because of high rates of resistance with DR-TB strains and higher incidence of ototoxicity.
STEP 3	Plus one of these Group 3: Fluoroquinolones levofloxacin moxifloxacin ofloxacin	Add a fluoroquinolone based on DST and treatment history. In cases where resistance to ofloxacin or XDR-TB is suspected, use a higher-generation fluoroquinolone, but do not rely upon it as one of the four core drugs.
STEP 4	Pick one or more of Group 4: Second-line oral bacteriostatic agents p-aminosalicylic acid cycloserine (or terizadone) ethionamide (or protionamide)	Add Group 4 drugs until you have at least four drugs likely to be effective. Base choice on treatment history, adverse effect profile and cost. DST is not standardized for the drugs in this group.
STEP 5	Consider use of these Group 5: Drugs of unclear role in DR-TB treatment clofazimine linezolid amoxicillin/clavulanate thioacetazone* imipenem/cilastatin high-dose isoniazid clarithromycin	Consider adding Group 5 drugs in consultation with an MDR-TB expert if there are not four drugs that are likely to be effective from Groups 1–4. If drugs are needed from this group, it is recommended to add at least two. DST is not standardized for the drugs in this group.

* Thioacetazone is contraindicated in HIV-positive individuals because of the serious risk of life-threatening adverse reaction.

Other considerations regarding the use of Group 1-5 drugs, as provided by the WHO:

Group 1:

Group 1 drugs should be used if there is good laboratory evidence and clinical history to suggest that a drug from this group is effective. If a Group 1 drug was used in a previous regimen that failed, its efficacy should be questioned even if the DST result suggests susceptibility. For patients with strains resistant to low concentrations of isoniazid but susceptible to higher concentrations, the use of high-dose isoniazid may have some benefit (when isoniazid is used in this manner it is considered a Group 5 drug; see below). The newer-generation rifamycins, such as rifabutin, have very high cross-resistance to rifampin.

Group 2:

All patients should receive a Group 2 injectable agent if susceptibility is documented or suspected. The guidelines suggest the use of kanamycin or amikacin as the first choice of an injectable agent, given the high rates of SM resistance in DR-TB patients. Amikacin and kanamycin are considered to be very similar and have a high frequency of cross-resistance. If an isolate is resistant to both streptomycin and kanamycin, or if drug resistance surveillance (DRS) data show high rates of resistance to amikacin and kanamycin, then capreomycin should be used.

The “intensive phase” of treatment for drug-resistant TB is based on the recommended duration of administration of the injectable agent and is guided by culture conversion. At a minimum, the WHO recommends that the injectable agent should be continued for at least 6 months total and for at least 4 months after the patient first becomes and remains sputum smear- or culture-negative. The use of an individualized approach that reviews the cultures, smears, X-rays and the patient’s clinical status may also help in deciding whether to continue an injectable agent longer than the above recommendation, particularly in the case of patients for whom the susceptibility pattern is unknown, effectiveness is questionable for an agent(s), or extensive or bilateral pulmonary disease is present.

Intermittent therapy with the injectable agent (three times a week) may also be recommended in patients in whom the injectable has been used for a prolonged period of time and when toxicity becomes a greater risk. If the patient was on an empirical regimen of five or six drugs, drugs other than the injectable can be considered for suspension once the DST results are available and the patient continues with at least three of the most potent agents.

Group 3:

All patients should receive a Group 3 medication if the strain is susceptible or if the agent is thought to have efficacy. Ciprofloxacin is no longer recommended to treat drug-susceptible or drug-resistant TB. While ofloxacin is commonly used, moxifloxacin and levofloxacin, are believed to be more effective and have similar adverse effect profiles.

Gatifloxacin is associated with serious cases of dysglycemia and new-onset diabetes. If gatifloxacin is used, it should undergo close monitoring and follow-up; gatifloxacin has been removed from the markets of many countries. For this reason, it has not been placed in the tables throughout the guidelines. Levofloxacin is, for the time being, the fluoroquinolone of choice until more data confirm the long-term safety of moxifloxacin. A later-generation fluoroquinolone is recommended for treatment of XDR-TB, although there is inadequate evidence on whether this is an effective strategy. Because the data on long-term use of fluoroquinolones are limited, vigilance in monitoring is recommended for all fluoroquinolones.

Group 4:

Group 4 medications are added based on estimated susceptibility, drug history, efficacy, and side-effect profile. Ethionamide or prothionamide

is often added; however, these drugs do have some cross-resistance with isoniazid. PAS may also be added first, given that the enteric-coated formulas are relatively well tolerated and it shares no cross-resistance to other agents.

When two agents are needed, cycloserine is used often in conjunction with ethionamide or protionamide or PAS. Since the combination of ethionamide or protionamide and PAS often causes a high incidence of gastrointestinal adverse effects and hypothyroidism, these agents are usually used together only when three Group 4 agents are needed: ethionamide or protionamide, cycloserine and PAS.

Terizidone is being used in some countries instead of cycloserine and is assumed to be as efficacious; however, there are no direct studies comparing the two drugs, and terizidone is therefore not yet recommended by WHO. The drugs in Group 4 may be started at a low dose and escalated over two weeks.

Group 5:

Group 5 drugs are not recommended by WHO for routine use in DR-TB treatment because their contribution to the efficacy of multidrug regimens is unclear. Although they have demonstrated some activity in vitro in animal models, there is little or no evidence of their efficacy in humans for the treatment of DR-TB. However, they can be used in cases where adequate regimens are impossible to design with the medicines from Groups 1–4. They should be used in consultation with an expert in the treatment of DR-TB. If a situation requires the use of Group 5 drugs, the guidelines recommend using at least two drugs from the group, given the limited knowledge of efficacy.

While thioacetazone is a drug with known efficacy against TB, it is placed in Group 5 because its role in DR-TB treatment is not well established. Thioacetazone has cross-resistance with some of the other anti-TB agents and thought overall to be a weak bacteriostatic drug. Thioacetazone is not recommended in HIV-positive individuals given the serious risk of adverse reaction that can result in Stevens-Johnson syndrome and death. People of Asian descent also have a higher incidence of Stevens-Johnson syndrome. Many experts feel that high-dose isoniazid can still be used in the presence of resistance to low concentrations of isoniazid (>1% of bacilli resistant to 0.2 µg/ml but susceptible to 1 µg/ml of isoniazid), whereas isoniazid is not recommended for high-dose resistance (>1% of bacilli resistant to 1 µg/ml of isoniazid).

Designing a Program Strategy:

The WHO recommends how to design a programs treatment strategy and is based on different situations in resource-constrained areas with limited access to DST. The strategy attempts to cover most situations; however, it may need to be adjusted to meet special circumstances. It assumes that DST of INH, RIF, the fluoroquinolones and the injectable agents is fairly reliable. It also assumes DST of other agents is less reliable and that basing individualized treatments on DST of these agents should be avoided.

Whenever possible, the guidelines recommend performing DST of injectable agents and a fluoroquinolone if MDR-TB is documented and treating according to the DST results:

Documented, or almost certain, <u>susceptibility</u> to a fluoroquinolone AND injectable agent	Start Category IV treatment consisting of: <ul style="list-style-type: none"> • an injectable agent • a fluoroquinolone • two Group 4 agents, with or without PZA.
Documented, or almost certain, <u>susceptibility</u> to a fluoroquinolone AND Documented, or almost certain, <u>resistance</u> to an injectable agent	Start Category IV treatment consisting of: <ul style="list-style-type: none"> • an injectable agent • a fluoroquinolone • three Group 4 agents, with or without PZA. <p>Use an injectable with documented susceptibility; if the strain is resistant to all, then use one for which resistance is relatively rare</p>
Documented, or almost certain, <u>resistance</u> to a fluoroquinolone AND Documented, or almost certain, <u>susceptibility</u> to an injectable agent	Start Category IV treatment consisting of: <ul style="list-style-type: none"> • an injectable agent • a fluoroquinolone • three Group 4 agents, with or without PZA. <p>Use a later-generation FQ</p>
Documented, or almost certain, <u>resistance</u> to a fluoroquinolone AND an injectable agent	Start Category IV treatment for XDR-TB

The role of surgery in the management of pulmonary DR-TB is also discussed by the WHO:

Large case-series analysis has shown resection surgery to be effective and safe under appropriate surgical conditions. It is considered an adjunct to chemotherapy and appears to be beneficial for patients when skilled thoracic surgeons and excellent postoperative care are available. It is not indicated in patients with extensive bilateral disease.

Resection surgery should be timed to offer the patient the best possible chances of cure with the least morbidity. Thus, the timing of surgery may be earlier in the course of the disease when the patient's risk of morbidity and mortality is lower, for example, when the disease is still localized to one lung or one lung lobe. In other words, surgery should not be considered as a last resort. Generally, at least two months of therapy should be given before resection surgery in order to decrease the bacterial infection in the surrounding lung tissue. Even with successful resection, an additional 12 – 24 months of chemotherapy should be given.

7.3.Duration of Treatment

Effective chemotherapy for TB didn't become available until the introduction of INH in the early 1950s and the early therapies, such as INH, SM, and PAS, required 18 to 24 months of treatment.⁶⁹ The British Medical Research Council (BMRC) in East Africa conducted the first large-scale multicenter study of short-course (6-month) regimens.⁷⁰ This study demonstrated that the addition of RIF or PZA to a base regimen of daily SM and INH increased the proportion of patients whose sputum cultures were negative by 2

⁶⁹ Medical Research Council. Long-term chemotherapy in the treatment of chronic pulmonary tuberculosis with cavitations. *Tubercle* 1962;43:201.

⁷⁰ East African/British Medical Research Council. Controlled clinical trial of four short-course (6-month) regimens of chemotherapy for treatment of pulmonary tuberculosis. *Lancet* 1973;i:1331--1339.

months after the initiation of treatment and significantly reduced the relapse rate. Moreover, the relapse rate of the short-course regimens was no greater than that of the standard 18-month regimen containing SM, INH, and thiacetazone (a drug used in many countries in place of PAS or EMB). Subsequent studies have refined the use of a 6-month regimen for drug-susceptible TB and regimens less than 6 months in duration have been shown to have unacceptably high relapse rates among patients with smear-positive pulmonary tuberculosis.^{71,72}

In the case when there is resistance to INH longer treatment is recommended. According to the ATS/CDC/ISDA guidelines, a regimen of RIF and EMB for 12 months with PZA during at least the initial 2 months has been shown to be effective. The guidelines also suggest a regimen of at least 12 to 18 months consisting of INH, EMB, and a fluoroquinolone supplemented with PZA during at least the initial 2 months, if RIF is not used. An injectable agent may also be included for the initial 2--3 months for patients with more extensive disease or to shorten the duration (e.g., to 12 months).⁷³ In the treatment of TB resistance to more than one drug, the optimal duration of treatment is thought to be for 24 months after the sputum culture becomes negative.⁷⁴ This duration of treatment is not based on rigorously documented studies, but observations that earlier discontinuation of treatment before this time increases the risk of reactivation.

The WHO recommends that the duration of treatment should be guided by culture conversion. The guidelines state that, at a minimum, treatment should last for at least 18 months after culture conversion. However, extension to 24 months may be indicated in patients defined as 'chronic cases' with extensive pulmonary damage.

7.4.Role of Drug Susceptibility Testing (DST)

Guidelines for the Treatment of Tuberculosis: American Thoracic Society, CDC, and Infectious Diseases Society of America, 2003.

According to the ATS/CDC/IDSA guidelines, antimicrobial susceptibility testing should be performed using a standard methodology, such as that recommended by the Clinical Laboratory Standards Institute (formerly National Committee for Clinical Laboratory Standards).⁷⁵

⁷¹ East Africa/British Medical Research Council. Controlled clinical trial of five short-course (4 month) chemotherapy regimens in pulmonary tuberculosis: second report of the 4th study. *Am Rev Respir Dis* 1981;123:165--170.

⁷² Singapore Tuberculosis Service/British Medical Research Council. Long-term follow-up of a clinical trial of 6-month and 4-month regimens of chemotherapy in the treatment of pulmonary tuberculosis. *Am Rev Respir Dis* 1986;133:779--783.

⁷³ American Thoracic Society, CDC, and Infectious Diseases Society of America. Treatment of Tuberculosis. *MMWR*. June 20, 2003;52(RR11);1-77.

⁷⁴ Iseman MD. Treatment of multidrug-resistant tuberculosis. *NEJM* 1993;29(11):784-91.

⁷⁵ American Thoracic Society, CDC, and Infectious Diseases Society of America. Treatment of Tuberculosis. *MMWR*. June 20, 2003;52(RR11);1-77.

In patients treated for drug-susceptible TB, relapses may occur with either drug-susceptible or –resistant strains of MTB. Therefore, microbiological confirmation the nature of the infecting strain is very important. Drug susceptibility tests should be repeated if sputum cultures remain positive for *M. tuberculosis* after 3 months of treatment or become positive after 1 month or longer of negative cultures.⁷⁶

The most recent CLSI document provides susceptibility testing methods for the primary drugs (i.e., INH, RIF, EMB, and PZA) and recommends testing of secondary anti-TB drugs on all isolates that are resistant to RIF or any two of the primary drugs. In addition, it notes that results of *in vitro* susceptibility testing of the primary drugs correlates well with clinical effectiveness in patients with TB, but that data concerning testing of secondary drugs is more limited.

The CLSI document further states:⁷⁷

The full panel of primary drugs for susceptibility testing of MTBC includes INH at two concentrations (critical and higher concentration), RIF, EMB, and PZA. This represents a combination of tests that provides the clinician with comprehensive information related to the four-drug therapy currently recommended for treatment of most patients in the United States with tuberculosis. Including PZA and a higher concentration of INH in the panel provides immediate additional information about the efficacy of four-drug therapy when resistance is encountered. The full panel of primary drugs may also provide sufficient information to avoid unnecessary secondary drug testing when a strain of MTBC is resistant only to INH, which is the most frequent pattern in the United States. Drug susceptibility testing with commercial shorter-incubation systems, however, is expensive, requiring that laboratories make decisions about cost-effective testing. Laboratory directors should consult with their pulmonary and/or infectious disease specialist and TB control officer when making decisions concerning reducing the number of drugs tested. The decision to test fewer or more (e.g., including streptomycin) drugs should be based on considerations of: 1) the patient population served; 2) prevalence of drug resistance; 3) standard drugs used for treatment within the community; and 4) the availability and timeliness of obtaining additional testing when resistance or drug intolerance is encountered. In many areas, for example, laboratories may consider testing a single, critical concentration of INH, RIF, and EMB only. State, provincial, and local public health laboratories serve as referral centers for mycobacterial testing, including drug susceptibility testing for MTBC. At a minimum, state and provincial public health laboratories should provide, or assure access to, the full panel of primary antituberculous drugs and secondary drugs. This reference service is necessary to provide continued surveillance of drug resistance and to rapidly augment testing for laboratories that may choose to test less than the full panel of primary drugs.

Whenever secondary drug testing is required, laboratories should avoid a “piecemeal” approach to providing clinicians with additional drug susceptibility test results. This is a particular concern, because currently most secondary drug testing is performed using the slower agar proportion method. If a laboratory routinely tests only the lower, critical concentration of INH (in addition to other primary drugs), any isolate of MTBC that is resistant to that concentration should also be tested to the higher concentration of INH. Whenever an isolate of MTBC is resistant to RIF or resistant to any two of the primary drugs, all secondary drugs (listed in Table 1) and a higher concentration of EMB should also be tested. If such testing is not done in-house, the isolate should

⁷⁶ American Thoracic Society. Diagnostic standards and classification of tuberculosis in adults and children. *Am J Respir Crit Care Med* 2000;161:1376--95.

⁷⁷ Clinical Laboratory Standards Institute. Susceptibility testing of Mycobacteria, Nocardiae, and other Aerobic Actinomycetes (2003) M24A, Vol 23 No 18.

immediately be forwarded to a public health or other referral laboratory. Isolates should be retained until results are available to complete reporting requirements. Additionally, for patients with resistant isolates, including resistance only to the lower, critical concentration of INH, referral to or consultation with a specialist in tuberculosis treatment should be considered."

According to a publication by Rich et al., drug susceptibility testing of second line drugs should be performed only in reference laboratories and should be limited to specimens from patients who 1) have had previous therapy, 2) are contacts of patients with drug-resistant TB disease, 3) have demonstrated resistance to RIF or to other first-line drugs, 4) have positive cultures after 3 months of treatment, or, 5) are from regions with a high prevalence of multiple drug-resistant (MDR) or extensively drug-resistant (XDR) TB.⁷⁸

The following recommendations regarding new diagnostic modalities are cited by the CDC:⁷⁹

Molecular beacons, phage-based assays, and line probe assays are three methods for rapidly detecting the presence of drug resistance, specifically to INH and RIF. These assays are expensive, require sophisticated laboratory support, need further study, and are not yet FDA-approved for use in the United States. Published results on the performance of the two assays suitable for direct use on samples, the INNO-LiPA Rif.TB kit (Innogenetics, Gent, Belgium) and FASTPlaque-TB (Biotec Laboratories Ltd., Ipswich, United Kingdom), have been inconsistent. Until results of ongoing validation and field testing of these rapid tests are available, conventional laboratory methods for culture and susceptibility testing should be pursued on all suspect clinical specimens.

WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis, 2008 and Drug Susceptibility Testing

The WHO guidelines state key recommendations regarding use of DST include:⁸⁰

- All patients suspected of DR-TB need access to laboratory services for adequate and timely diagnosis of DR-TB;
- Laboratories should develop proficiency to isoniazid and rifampicin as a minimum and then consider DST of other drugs
- Laboratories should develop DST of the fluoroquinolones and second-line injectable agents where adequate capacity and expertise exist

However, the guidelines also state that countries vary greatly in their access to reliable mycobacterial laboratories, and many do not have regular access to DST. Delays in treatment while awaiting DST can result in increased morbidity and mortality, as well as longer periods of infectiousness.

Therefore, the inability to do routine DST in all patients should not be a barrier for patients that need Category IV treatment. Standardized regimens are recommended even in countries where reliable DST is available for the following reasons:

⁷⁸ Rich ML, Socci AR, Mitnick CD, et al. Representative drug susceptibility patterns for guiding design of retreatment regimens for MDR-TB. *Int J Tuberc Lung Dis* 2006;10:290--6.

⁷⁹ Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-positive Adults and Adolescents. *MMWR*, March 24, 2009;58(Early Release);1-198.

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr58e324a1.htm?s_cid=rr58e324a1_e

⁸⁰ World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency Update 2008. WHO/HTM/TB/2006.402. Geneva: WHO, 2008:

http://www.who.int/tb/publications/global_report/2008/en/

- Interpretation of DST to some of the first- and second-line drugs is difficult and could mislead regimen design. Standardized regimens can give guidance to clinicians and prevent basing decisions on DST that is not reliable.
- These guidelines do not recommend using DST of ethambutol, pyrazinamide and the drugs in Groups 4 and 5 to base individual regimen design.
- Turnaround time for many culture-based DST methods is long. In general, patients at increased risk for DR-TB should be placed on an empirical Category IV regimen until DST results are available.
- The laboratory may not perform DST of certain drugs, or may perform them at different times. Results from rapid methods (molecular) may be available within days, but only for certain first-line drugs such as isoniazid and rifampicin. Many laboratories perform second-line DST only after resistance to first-line drugs is confirmed.

The reasons for lack of reliability in DST are described by the WHO document:

Procedures for microscopy, culture and DST of first-line antituberculosis drugs have been standardized internationally and are well described in the literature, with consensus on methodologies, critical drug concentrations, and reliability and reproducibility of testing.

On the other hand, surveys on practices for second-line DST in specialized laboratories and a few multi-centre laboratory studies have revealed important methodological differences. No studies have systematically evaluated all available DST methods for all available second-line drugs, established critical concentrations for all available second-line drugs, or evaluated a large number of clinical isolates for microbiological and clinical end-points. Most importantly, the correlation of in vitro DST results with clinical outcome has not been established, and the prognostic value of in vitro resistance to second-line antituberculosis drugs is therefore not known.

...The accuracy of DST (performed under optimal circumstances) varies with the drug tested: for the first-line antituberculosis drugs, DST is most accurate for rifampicin and isoniazid; it is less reliable and reproducible for streptomycin, ethambutol and pyrazinamide.

Testing of in vitro susceptibility of second-line antituberculosis drugs is much more problematic, as outlined in WHO policy guidance on second-line DST: aminoglycosides, polypeptides and fluoroquinolones have been tested in different laboratory environments and shown to have relatively good reliability and reproducibility. Data on the reproducibility and reliability of DST for the other second-line drugs are much more limited, have not been established or the methodology for testing does not exist.

Susceptibility testing of second-line drugs is hampered by technical difficulties due to in vitro drug instability, drug loss due to protein binding, heat inactivation, incomplete dissolution, filter sterilization and/or varying drug potency. Moreover, the critical concentration defining resistance is often very close to the minimal inhibitory concentration (MIC) required to achieve antimycobacterial activity, increasing the probability for misclassification of susceptibility or resistance and leading to poor reproducibility of DST results. In addition, laboratory technique, medium pH, incubation temperature and incubation time may also affect DST results.

As mentioned above, the critical concentration of some drugs is close to the minimal inhibitory concentration for wild susceptible strains and, thus, drug-susceptibility testing is prone to yield poorly reproducible results.

This concept is explained further by Kim et al.;⁸¹

The absorption, the diffusion into the lesions and the maintenance level of a drug are all important factors for the emergence of drug resistance. INH and RFP, whose susceptibility testing results are fairly reliable, show a peak serum concentration over 100-times higher than the MIC, and it is certainly possible to maintain them at a fairly high concentration in the lesions throughout the treatment, unless the patient interrupts drug intake. Conversely, peak serum levels of cycloserine, EMB, ciprofloxacin, ofloxacin and ETH are closer to MICs. As a consequence, in some patients, the period of inhibitory concentration of the drug within the lesions may be short and/or the drug level may remain subinhibitory during most of the time. In general, DST results to the latter drugs display low reliability.

Regarding the use of rapid diagnostic tests for DST, the WHO states the following:⁸²

Case-finding strategies can be greatly enhanced with rapid drug-resistance testing, which significantly improves the ability to identify earlier cases of DRTB that can be isolated and started on treatment.

Rifampicin is the most potent antituberculosis drug of the first-line regimen, and rifampicin resistance most commonly occurs with concomitant isoniazid resistance. A positive rapid test for rifampicin resistance is a strong indicator that a patient may have MDR-TB, while a negative test makes a final diagnosis of MDR-TB highly unlikely.

... Novel technologies for rapid detection of drug resistance are under development. Most are in early development phase, undergoing laboratory validation or in early stages of large-scale field studies to assess their feasibility, cost effectiveness and cost benefit. Technologies focused on rapid rifampicin resistance testing as a proxy for MDR-TB testing are most advanced.

... Several tests for rapid detection of rifampicin resistance have been validated in laboratory-based studies. The use of rapid rifampicin resistance testing is recommended in high-risk MDR-TB settings (including high-burden HIV settings); however, confirmation of MDR-TB by conventional DST is still regarded as the gold standard, and adequate laboratory capacity to ensure a quality-assured diagnosis of MDR-TB therefore remains a fundamental requirement.

The WHO document also provides an algorithm on the use of rapid DST testing for identification and initial management of patients suspected of TB who are at increased risk of DR-TB. The algorithm relies on determining the risk of drug resistance and involves HIV testing of all TB suspects, sputum smear microscopy and results from rapid sensitivity testing for at least RIF. It also includes the indications for the use of empirical treatment regimens for DR-TB while awaiting more complete DST results.

Immunological and Molecular Markers of Response

Immunological Markers

Immunological techniques and genomic analysis have accelerated progress in the characterization of immunologic markers, particularly with the discovery of a new

⁸¹ Kim SJ. Drug-susceptibility testing in tuberculosis: methods and reliability of results. *European Respiratory Journal* 2005;25:564-9.

⁸² World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency Update 2008. Document no. WHO/HTM/TB/2006.402. Geneva: WHO, 2008: http://www.who.int/tb/publications/global_report/2008/en/

generation of in-vitro tests of cell-mediated immunity: T-cell based interferon-assays.²⁵ These assays quantify the release of interferon from T cells in response to stimulation by specific *M. tuberculosis* antigens such as early secreted antigenic target 6 (ESAT6) and culture filtrate protein 10 (CFP10). These tests have mainly been investigated for diagnostic purposes using blood and lung bronchoalveolar lavage. These assays could be useful as a biomarker, particularly in extrapulmonary tuberculosis, if they correlate with mycobacterial load. However, the usefulness of such a test is severely limited by the lack of an immunological marker of tuberculosis cure. There are few data from clinical trials to assess the use of these tests in monitoring response.

Molecular Markers

Molecular markers provide a more rapid assessment of mycobacterial burden than culture. Early studies compared DNA detection by PCR with microscopy and culture, and PCR produced a positive result sooner and was more sensitive than other methods. Detection was prolonged, however, because of DNA detection from non-viable organisms. As with DNA, levels of ribosomal RNA (rRNA) also fall slowly, and viable and non-viable organisms cannot be distinguished. Messenger RNA (mRNA), however, could be used as a marker of mycobacterial viability; one study showed a correlation between loss of mRNA with treatment, and sputum culture clearance.⁸³ mRNA detection is, however, only moderately sensitive, which might limit its use as a biomarker. Other molecules, such as *M. tuberculosis* antigen 85, may predict relapse as they are expressed in a sustained manner in sputum during treatment.⁸⁴

7.5. Treatment of Drug-Resistant TB in Patients Co-Infected with HIV: Considerations with Anti-Retroviral Drugs

The recommended treatment for drug-resistant TB is the same for HIV-positive as for non-HIV-positive patients, except for the use of thioacetazone, which is not recommended for use in HIV-seropositive patients. However, treatment is much more difficult and adverse events more common in HIV patients. Deaths during treatment, caused by TB itself or by other HIV-related diseases, are more frequent in HIV-positive patients, particularly in the advanced stages of immunodeficiency.

The use of anti-retroviral therapy (ART) in HIV-positive patients with TB improves survival and slows progression to AIDS. However, initiation of ART in HIV-positive patients with drug-susceptible or drug-resistant TB can be complicated by drug-drug interactions and adverse events that may lead to loss of efficacy or interruption of both TB and/or HIV therapy. In general, HIV patients have a higher rate of adverse drug reactions to both TB and non-TB medications.

⁸³ Hellyer TJ, DesJardin LE, Hehman GL, Cave MD, Eisenach KD. Quantitative analysis of mRNA as a marker for viability of *Mycobacterium tuberculosis*. *J Clin Microbiol* 1999;37(2):290-95

⁸⁴ Wallis RS, Perkins MD, Phillips M, Joloba M, Demchuk B, Namale A, Johnson JL, Williams D, Wolski K, Teixeira L, Dietze R, Mugerwa RD, Eisenach K, Ellner JJ. Induction of the antigen 85 complex of *Mycobacterium tuberculosis* in sputum: a determinant of outcome in pulmonary tuberculosis treatment. *J Infect Dis* 1998; 178: 1115–21

The following is an excerpt from the **CDC Guidelines on Treatment of Opportunistic Infections in HIV Patients** regarding concomitant use of ART:⁸⁵

ART in the Management of TB Disease

The treatment of TB can be complicated by drug interactions with the rifamycins and overlapping toxicities associated with antiretrovirals (ARVs) and anti-TB drugs when therapy for both HIV and TB infections is concomitantly administered. Both RIF and rifabutin induce CYP3A enzymes, and although rifabutin is not as potent an inducer as RIF, it is a substrate, leading to drug interactions with the PIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs) when these agents are concomitantly administered with the rifamycins; such administration might result in increased metabolism and suboptimal levels of ARVs.

Compared with PI-based regimens, NNRTI-based regimens have fewer interactions with RIF-based TB therapy. Rifabutin is an alternative to RIF and can be administered with PIs or NNRTIs with appropriate dose adjustments. Concomitant use of RIF with ritonavir-boosted PIs has been shown to result in subtherapeutic levels of the PI. Use of ritonavir-boosted saquinavir with RIF was associated with a high incidence of hepatotoxicity in a pharmacokinetic study using healthy volunteers. RIF should not be used in patients on PI-based regimens, with or without ritonavir-boosting. For patients undergoing treatment for active TB, starting ART with either an efavirenz- or nevirapine-based regimen is preferred because these NNRTIs have fewer interactions with RIF; dosage adjustments for these NNRTIs might be needed for persons weighing more than 60 kg. Delavirdine should not be used with either RIF or rifabutin.

If rifabutin is used in place of RIF, dosage reduction is required with boosted-PI regimens. Efavirenz decreases the levels of rifabutin, and the dose of the latter might have to be increased. Nevirapine does not affect the levels of rifabutin sufficiently to merit adjustment of the rifabutin dose. Underdosing of ARVs or rifabutin can result in selection of HIV drug-resistant mutants or acquired rifamycin resistance, respectively, whereas overdosing of rifabutin might result in dose-related toxicities such as neutropenia and uveitis. Because interpatient variations in the degree of enzyme induction or inhibition can occur, the use of therapeutic drug monitoring for levels of rifabutin, PIs, or NNRTIs might help to adjust dosing for individual patients.

HIV nucleos(tide) analogs and the fusion inhibitor enfuvirtide are not affected by the CYP enzymes and can be used with the rifamycins. Results of ongoing drug-drug interaction studies predict that the combination of RIF (and possibly rifabutin) will result in decreased levels of maraviroc, raltegravir, and elvitegravir. Until data are available to guide dose adjustment, these drugs in combination should be avoided or used with extreme caution. Available NNRTIs and PIs do not have clinically significant drug interactions with other first- and second-line anti-TB drugs; thus, when rifamycins cannot be administered because of toxicity or resistance (MDR or XDR *M. tuberculosis* strains), ART regimens should be selected on the basis of other factors appropriate to the patient.

Optimal Timing of Initiation of ART in ART-Naïve Patients with Active TB

For ART-naïve, HIV-positive persons who are diagnosed with active TB, anti-TB treatment must be started immediately. The optimal timing of initiation of ART in this setting is not clear. Options include simultaneous TB and ART or treatment of TB first with delay of ART by several weeks to

⁸⁵ Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-positive Adults and Adolescents. MMWR, March 24, 2009;58(Early Release);1-198.
<http://www.aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?ClassID=4&GuidelineID=211&MenuItem=Guidelines&Search=Off>

months. A positive aspect of starting both regimens simultaneously is the possible prevention of progressive HIV disease and reduction in morbidity or mortality associated with TB or other OIs. A negative of this approach is the possibility of overlapping toxicities, drug interactions, a high pill burden, and the possibility of developing IRIS or a paradoxical reaction. These factors must be weighed carefully when choosing the best time to start ART in individual patients.

Several randomized clinical trials are under way to address the optimal timing of initiation of ART in persons being treated for active TB, but the results will not be known for several years. Pending these results, certain specialists determine when to start ART based on the immunologic status of the patients (339,351,352). For patients with a CD4+ count <100 cells/μL, ART should be started after ≥ 2 weeks of TB treatment to reduce confusion about overlapping toxicities, drug interactions (339), and the occurrence of paradoxical reactions or IRIS [Immune Reconstitution Inflammatory Syndrome]. For persons with a CD4+ count of 100 - 200 cells/μL, certain specialists would delay ART until the end of the 2-month intensive phase of anti-TB treatment. In those with a sustained CD4+ count > 200 cells/μL, ART could be started during the anti-TB maintenance phase and for those with a CD4+ count > 350 cells/μL, after finishing anti-TB treatment. In one study, paradoxical reactions occurred in almost all HIV-positive patients with TB and a CD4+ count <100 cells/μL who started ART within the first 30 days of TB therapy. However, other studies suggest this approach might prevent HIV disease progression or death. In a small, prospective, nonrandomized study of 49 HIV-positive patients from Brazil (348) treated with a RIF-based anti-TB regimen and efavirenz-based ART, morbidity and side effects of medications in patients who started ART 3 weeks after initiation of TB treatment were reduced, compared with those who started ART and anti-TB treatment simultaneously. Furthermore, simultaneous anti-TB and anti-HIV treatment did not reduce overall mortality.

When TB occurs in patients already on ART, treatment for TB must be started immediately, and ART should be modified to reduce the risk for drug interactions and maintain virologic suppression. When TB occurs in the setting of virologic failure, ART drug-resistance testing should be performed and a new ART regimen constructed to achieve virologic suppression and avoid drug interactions with the anti-TB regimen administered.

The WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis also discuss timing of ART in the ART-naïve patient starting anti-TB therapy for DR-TB in HIV co-infected patients:⁸⁶

The use of ART in HIV-positive patients with TB improves survival for both drug-resistant and susceptible disease...cohorts of patients treated for DR-TB without the benefit of ART have experienced mortality rates often exceeding 90%. However, the likelihood of adverse effects could compromise the treatment of either HIV or DR-TB if both treatments are started simultaneously. On the other hand, undue delay in the start of ART could result in significant risk of HIV-related death among patients with advanced disease. The optimal timing for the introduction of ART in patients receiving TB treatment is unknown...[The table below is] based on WHO guidelines for the treatment of HIV infection in adults and adolescents, provides recommendations for initiating ART in relationship to starting therapy for DR-TB.

⁸⁶ World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency Update 2008. Document no. WHO/HTM/TB/2006.402. Geneva: WHO, 2008: http://www.who.int/tb/publications/global_report/2008/en/

CD4 cell count	ART Recommendations	Timing of ART in Relation to Start of DR-TB Treatment
CD4 < 200 cells/mm ³	Recommend ART	At two weeks or as soon as DR-TB treatment is tolerated
CD4 between 200 and 350 cells/mm ³	Recommend ART	After eight weeks ^a
CD4 > 350 cells/mm ³	Defer ART ^b	Re-evaluate patient monthly for consideration of ART start. CD4 testing is recommended every three months during DR-TB treatment.
Not available	Recommend ART ^c	Between two and eight weeks

^aClinical evaluation may prompt earlier initiation of ART.

^bART should be started if other non-TB stage 3 or 4 events are present.

^cThis recognizes that some patients may be prematurely placed on life-long ART

...There are two issues to consider in patients who are diagnosed with DR-TB while on ART. The first is whether modification of ART is needed due to drug–drug interactions or to decrease the potential of overlapping toxicities...The second issue is whether the presentation of active DR-TB in a patient on ART constitutes ART failure...If ART failure has been diagnosed, it is not recommended to begin a new second-line ART regimen at the same time as initiation of a DR-TB regimen. Instead, continue the present ART regimen and switch to the second-line ART regimen 2–8 weeks after the start of DR-TB treatment.

7.6. Treatment Failure in Drug-Resistant TB

According to the WHO guidelines, patients who do not show signs of improvement after four months of treatment are at risk for treatment failure.⁸⁷ In all patients who show clinical, radiographic or bacteriological evidence of progressive active disease, or reappearance of disease after month 4 of treatment, should be considered as being at high risk for treatment failure.

In patients who are known to have adhered to treatment, the treatment regimen should be reviewed in relation to medical history, contacts and all DST reports. If the regimen is deemed inadequate, a new regimen should be designed.

In addition, bacteriological data should be reviewed. Smear and culture data can be considered evidence that a patient is not responding to therapy. The WHO guidelines state that one single positive culture in the presence of an otherwise good clinical response can be caused by a laboratory contaminant or error. In this case, subsequent cultures that are negative or in which the number of colonies is decreasing may help prove that the apparently positive result did not reflect treatment failure. Positive smears with negative cultures may be caused by the presence of dead bacilli and therefore may not indicate treatment failure. Repeated culture- and smear-negative results in a patient with clinical and radiographical deterioration may indicate that the patient has a disease other than MDR-TB.

⁸⁷ World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency Update 2008. Document no. WHO/HTM/TB/2006.402. Geneva: WHO, 2008: http://www.who.int/tb/publications/global_report/2008/en/

Other illnesses that may decrease absorption of medicines (e.g. chronic diarrhea) or may result in immune suppression (e.g. HIV infection) should be excluded.

The WHO document states:

MDR-TB treatment often consists of a treatment cycle; if no response is seen, reassessment of the regimen and treatment plan and formulation of a new plan of action are necessary. Patients who have persistent positive smears or cultures at month 4 but who are doing well clinically and radiographically may not require a regimen change. Whenever a regimen change is indicated because of treatment failure, a new regimen is started (with at least four effective drugs) and options for adjunctive treatment – most commonly surgery – can be considered. Adding one or two drugs to a failing regimen should be avoided. Changes in treatment can be made as early as 4–6 months if conversion is not seen and if there is clinical deterioration.

It takes 3–4 months to evaluate whether a change in treatment plan has been effective. If the patient continues to deteriorate despite the measures described in the previous section, treatment failure should be considered. There is no single indicator to determine whether a treatment regimen is failing. Although there is no simple definition for treatment failure, there often comes a point during the treatment when it becomes clear that the patient is not going to improve. Signs indicating treatment failure include:

- persistent positive smears or cultures past month 8–10 of treatment;
- progressive extensive and bilateral lung disease on chest X-ray with no option for surgery;
- high-grade resistance with no option to add two additional agents;
- overall deteriorating clinical condition that usually includes weight loss and respiratory insufficiency.

It is not necessary for all of these signs to be present to identify failure of the treatment regimen. However, a cure is highly unlikely when they are all present.

8. Clinical Trial Considerations for MDR-TB

The following discussion pertains to clinical trials of pulmonary MDR-TB, defined as disease involving the lung parenchyma. Non-clinical and early phase clinical development considerations will not be addressed. **See also Appendix C which contains the FDA Concept Paper -- Pulmonary Tuberculosis: Developing Drugs for Treatment**

8.1. General Drug Development Plan

In general, two adequate and well-controlled clinical trials are needed to establish effectiveness of a drug product (21 CFR 314.126) and this holds true for the treatment indication of pulmonary tuberculosis due to resistant organisms. A single adequate and well-controlled study can also be used to demonstrate effectiveness, in which case the FDA must also rely on pertinent information from other adequate and well-controlled

studies, such as studies of other doses and regimens, of other dosage forms, in other stages of disease, in other populations, or of different endpoints.⁸⁸

8.2. Study Design

Clinical trials must comply with applicable laws, regulations, and standards of care.^{89,90,91}

Trials should be double-blind unless there is compelling justification why blinding cannot be accomplished. Methods of blinding include the use of matching placebos, matching active comparators, or over-encapsulation.

To demonstrate efficacy, trials for drug-resistant TB should generally be designed as to show superiority. Demonstration of non-inferiority may be challenging; if such trials are conducted, a justification for a non-inferiority margin needs to be provided.

One possible design is a two-arm trial where an investigational drug plus a background regimen is directly compared to placebo plus a background regimen. Efficacy can be demonstrated by showing superiority of the investigational drug plus a background regimen over the placebo plus a background regimen. Patients in both arms will receive a background regimen predicted to be active based on epidemiologic information and susceptibility testing data when available. Placebo should be added to the background regimen in the comparator arm to maintain blinding. It is anticipated that the background regimen will be optimized based on the susceptibility profile of the individual patient's infecting strain of mycobacteria or on epidemiologic data; the regimen would be expected to include 3-4 drugs with in vitro activity against the mycobacteria.

In addition to the add-on clinical trial design described above, there may be other designs or variations of the above design that may be informative trial designs for evaluating the safety and efficacy of an investigational drug for the treatment of drug-resistant TB, such as dose-response. Dose-response trials where a higher dose (or more intensive regimen) is found to be superior to a lower dose (or less intensive regimen) are another approach to demonstrate efficacy. Efficacy trials that evaluate two investigational drugs should use a factorial design.

8.3. Fixed Combination Drugs

Trials evaluating a fixed-combination drug for the treatment of tuberculosis should also address the regulation on fixed-combination prescription drugs under 21 CFR 300.50. This regulation states that two or more drugs may be combined in a single dosage form

⁸⁸ See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products* (www.fda.gov/cder/guidance/1397fnl.pdf).

⁸⁹ See 21 CFR parts 50, 56, and 312.

⁹⁰ Human Subject Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application, 2008, *Federal Register*, Vol. 73, No. 82, pg. 22801-13.

⁹¹ See the ICH guidance for industry *E6 Good Clinical Practice: Consolidated Guidance* (<http://www.fda.gov/cder/guidance/index.htm>).

when each component makes a contribution to the claimed effect and the dosage of each component is such that the combination is safe and effective. Therefore, factorial design trials should be conducted to evaluate each of the components of the dosage form separately.

8.4. Choice of Comparator

It is anticipated that most trials of drug-resistant TB will be placebo controlled and that all study subjects will also be given a background regimen that has been optimized for each patient based on susceptibility test results for the individual patient's infecting strain of mycobacteria. Optimized background regimens (OBR) should represent standard of care and follow treatment guidelines.^{92,93} Initially OBR regimens should be based on epidemiologic information on susceptibility and then be modified when results from susceptibility testing are available; in general, patients should be on 3 to 4 drugs to which there is *in vitro* susceptibility.^{94,95}

Studies should be designed to capture detailed information on the OBR regimen and standardized criteria for how and when any changes (i.e., based on the results of drug susceptibility testing) can be made to the regimen should be addressed within the protocol. Both treatment arms of the trial should be handled consistently to prevent differential handling of by trial arm leading to a biased trial result. Provisions should also be made available, and pre-specified in the protocol, for alternative treatment in the setting of clinical or microbiological failure, or when there are serious adverse reactions requiring the termination of one or more drugs.

If local standard-of-care drugs are used in clinical trials conducted outside the US which are not FDA-approved drugs or are non-US approved formulations of FDA-approved drugs, sponsors should provide data to demonstrate the identity, strength, quality, uniformity of content and stability of the comparator drugs.

8.5. Trial Duration

Generally, treatment regimens are given for 18 to 24 months. Trials should be of sufficient length in order to be able to assess for recurrence of clinical symptoms or microbiologic findings following completion of therapy. The duration of observation following completion of treatment may need to be balanced by the loss to follow-up in these trials of multi-year duration. The determination of timing of relapse in clinical

⁹² Treatment of Tuberculosis. American Thoracic Society, CDC, and Infectious Diseases Society of America. Chapter 9, MMWR Vol 52. No. RR-11

⁹³ Guidelines for the programmatic management of drug-resistant tuberculosis. Chapter 7. World Health Organization. WHO/HTM/TB/2006.361

⁹⁴ American Thoracic Society, Centers for Disease Control, and Infectious Diseases Society of America, 2003, Treatment of Tuberculosis, MMWR, 52(RR-11): 1-77.

⁹⁵ World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency Update 2008. Document no. WHO/HTM/TB/2006.402. Geneva: WHO, 2008: http://www.who.int/tb/publications/global_report/2008/en/

trials is a topic deserving additional consideration and discussion. See Section 4.2 on “Early Endpoints: Predictors of Treatment Outcome” and Section 9 “Conclusions and Discussion for the Advisory Committee.”

8.6. Trial Population

Trials may be designed to enroll patients at risk for drug-resistant disease based upon epidemiological risk factors, or enroll patients with known drug-resistant TB that require a change to a new antimycobacterial regimen. It is likely that patients will be randomized and enrolled before standard drug susceptibility test results are available. If rapid diagnostic tests are used for determining drug susceptibility and patient eligibility, these results should be subsequently confirmed by culture. Protocols should specify how patients will be handled once drug susceptibility results are available, both in the conduct of the trial and in the analysis of the trial results.

Enrichment strategies for identifying patients with drug-resistant disease could include screening of contacts of drug-resistant TB cases, patients from areas with a high prevalence of drug resistance, patients relapsing after previous treatment, and patients failing standard TB therapy.

Patients should have clinical signs and symptoms of pulmonary disease, in addition to microbiologic confirmation. Clinical signs and symptoms should include a combination of chest radiograph findings (e.g., cavitary lesion or lesions, apical infiltrates, hilar lymphadenopathy, or a new infiltrate) and cough, hemoptysis, fever, pleuritic chest pain, weight loss, or night sweats.

8.7. Efficacy Endpoints

The primary endpoint for trials of investigational drugs to treat drug-resistant TB should be clinical and microbiological cure. Clinical cure is defined as complete resolution of clinical signs and symptoms of tuberculosis present at baseline and absence of any new clinical signs or symptoms.

Definition of microbiologic cure may vary, but one example would be the following based upon the WHO guidelines:⁹⁶

A Category IV patient who has completed treatment and has at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment. If only one positive is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart.

An example of clinical and/or microbiological failure would be defined as:

⁹⁶ World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency Update 2008. Document no. WHO/HTM/TB/2006.402. Geneva: WHO, 2008: http://www.who.int/tb/publications/global_report/2008/en/

- clinical progression of pulmonary disease or a new focus of extrapulmonary disease that requires either a change in antimycobacterial therapy or unanticipated surgical intervention
- Signs and symptoms of active tuberculosis (pulmonary or new onset of extrapulmonary), including radiographic worsening compared to baseline findings, resulting in re-initiation of antimycobacterial therapy during follow-up⁹⁷
- Death during treatment or follow-up
- A sputum culture with growth of *M. tuberculosis*:
 - After a specific time point defined in the trial
 - Failure to achieve a negative culture that results in a change in antimycobacterial therapy
 - Any growth of *M. tuberculosis* from an extrapulmonary site during the trial

Patients considered a clinical or microbiological failure during treatment should have therapy altered as appropriate; however, these patients should continue to be followed per protocol.

Relapse following microbiologic cure during and following treatment should also be assessed as an endpoint in clinical trials based on clinical and microbiologic findings. In the case of new microbiologic findings in patients who were previously documented as cured, attempts should be made to compare new isolates with baseline isolates to distinguish between relapse and re-infection using standardized methods.⁹⁸ The method used should be standardized and validated for differentiating relapse from new infection.

The presence or absence of clinical symptoms should also be captured as they provide the basis on which to conclude that patients who are not able to produce sputum on follow-up could be considered as remaining disease-free. During the follow-up period of a clinical trial patients should be assessed routinely, and on a for-cause basis, for the reappearance of clinical constitutional symptoms (i.e., weight loss, fever), as well as for routine microscopy of sputum. Causes other than pulmonary MDR-TB for the re-appearance of clinical symptoms should be investigated. Chest radiographs obtained at the end of treatment may help predict those patients who are at higher risk for relapse, based upon residual lung damage. Efforts should be made to distinguish relapse from reinfection. The total recurrence rate and the recurrence rate corrected for re-infection at the end of the observation period should be assessed in the patient population that initially achieved a clinical and microbiological cure at end of treatment.

⁹⁷ In some circumstances there may be brief re-initiation of antituberculosis therapy while there is diagnostic uncertainty whether relapse has occurred, but therapy is subsequently stopped when an alternative diagnosis is established. Protocols should define the duration of retreatment therapy that will be used to define clinical failure to avoid labeling patients in this situation as failures.

⁹⁸ In recent years molecular tests have been developed for the detection of various *M. tuberculosis* strains, identifying mutations, and assessing drug resistance in different geographic areas. These methods are mostly based on polymerase chain reaction using a small amount of DNA. However, these methods have not been standardized and validated for differentiating relapse from new infection. Details of the methods used and the performance characteristics of the assay in the laboratory where actual testing is done should be provided.

Timing for the assessment of clinical and microbiologic response during treatment and in the observation period of the trial are topics deserving additional consideration and discussion in trials of drug-resistant TB. See Section 4.2 on “Early Endpoints: Predictors of Treatment Outcome” and Section 9 “Conclusions and Discussion for the Advisory Committee.”

8.8. Accelerated Approval (Subpart H) Considerations

Approval under 21 CFR 314.500, subpart H, Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses, may be applicable to drugs developed for the treatment of drug-resistant tuberculosis if they are shown to provide meaningful therapeutic benefit over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.

In the case of drug-resistant TB, a potential surrogate endpoint to support accelerated approval would be conversion of sputum culture to no growth with a corresponding improvement in a clinical endpoint, such as clinical signs and symptoms (see Section XX for more discussion). When a drug is approved under 21 CFR 314.510 of Subpart H, sponsors are required to complete clinical trials to confirm the clinical benefit.⁹⁹ Therefore, trials should be designed to assess long-term clinical outcome (i.e., mortality and/or relapse of disease), as well as to continue to evaluate safety, for some period following the completion of therapy. Additional trials to confirm clinical benefit may also be warranted.

8.9. Analysis Populations

Similar to most other clinical trials, analysis populations in drug-resistant TB trials should be defined as follows:

- Intent to treat (ITT): all randomized patients.

⁹⁹ See 21 CFR 314.510, Approval Based on a Surrogate Endpoint or on an Effect on a Clinical Endpoint other than Survival or Irreversible Morbidity.

- Modified intent to treat (MITT): all randomized patients with a positive culture for *M. tuberculosis* from a pretreatment sample documenting a drug-resistant phenotype. The MITT population for the primary analysis should be defined *a priori*.
- Per protocol: all randomized patients with a positive culture from a pretreatment sample and achieving a pre-specified level of compliance with the protocol (e.g., presence at follow-up visits and adherence to dosing regimens).

Efficacy should be assessed in the MITT analysis population, with safety assessed primarily in the ITT population. In addition, consistency of the results for efficacy should be evaluated in the ITT and per-protocol populations. If there are notable differences between outcomes for the ITT and per-protocol populations, reasons for these differences should be investigated and stated in the trial report. Loss to follow-up should be minimized because this should result in a better estimate of drug efficacy.

The comparison of the proportion of patients with a clinical and microbiological cure at the completion of the observation period should be the primary efficacy analysis. Patients who are lost to follow-up, have died, or have recurrent tuberculosis should be analyzed as failures in the primary analysis.

In patients with recurrent tuberculosis, the ability to distinguish between relapse and re-infection would be an important consideration.

The use of unapproved diagnostic tests to select patients with drug-resistant TB may have unintended consequences for labeling of both the test device and the drug. Sponsors are encouraged to seek early consultation with the Agency when the use of an investigational device to define the population for inclusion are considered.¹⁰⁰

8.10. Missing Data

Clinical trials should, in general, plan to follow patients for occurrence of relapse (i.e., clinical and microbiological efficacy endpoints) after treatment completion. It is unclear exactly how long and how often subjects should be followed. In general, the analysis population of greatest interest in the determination of efficacy contains all randomized subjects with a positive culture for MDR-TB at the time of randomization. While this population preserves the randomization performed at entry into the study and is the population least subject to bias, analysis of this population will be complicated by the presence of missing data for late clinical and microbiological endpoints. Missing data can be due to subjects being lost to follow-up, having died, or having become re-infected. Note that typically all-cause mortality would be considered as a failure in the analysis of MDR-TB studies.

Any clinical trial protocol should include procedures for investigators to maximize data collection from all study subjects in order to minimize losses to follow up and missing

¹⁰⁰ <http://www.fda.gov/oc/combination/guidance.html>

data during this time period. Given that some missing data will occur, however, the protocol should state how missing data will be handled in the analysis. Additional methods of analyzing missing data should be included in the protocol or data analysis plan as secondary analyses; consistency among the various methods would be expected and would help ensure lack of sensitivity of the study conclusions to the type of method chosen. Note that missing data may confound the determination of efficacy. Significant amounts of missing data may render study results inconclusive. Rates of missing data by treatment arm should be compared and, if differences exist, should be further explored and discussed in the study report. Every effort should be made to minimize the loss to follow-up for the duration of the study because this should result in a better estimate of drug efficacy.

It is understood that the longer the follow-up period for assessing the primary endpoint the larger the number of subjects will be who have missing data. In considering the most appropriate time point for assessing efficacy of the trial, the rate of recurrence over time as well as ability to follow all subjects should be considered. It is important that the limitations of the data and ability to draw conclusions when too much missing data exists be understood.

8.11. Safety Considerations

To provide sufficient data on the safety of an investigational drug, the number of patients to be studied at the proposed dose and duration depends on a variety of factors including the risk-benefit for the indication, nonclinical toxicology concerns, clinical pharmacology findings, and clinical safety findings. Because drug-resistant TB is treated with a multiple-drug regimen, it is important that there is sufficient safety information be collected using the drug as part of the anticipated clinical regimen.

Study of special populations (i.e., geriatric patients, patients with renal insufficiency, and patients with hepatic impairment) should be included in the clinical safety database. Because of the high incidence of tuberculosis in patients co-infected with HIV, patients with HIV also should be included as part of the safety database.

The evaluation of the safety profile of an investigational drug for treating drug-resistant TB can be challenging because it is administered along with other antimycobacterial drugs and other concomitant medications (e.g., antiretroviral therapy for HIV) in patients who often have co-morbid conditions. Exploratory analyses of safety based on comparisons between patients that did and did not receive specific co-administered drugs may be informative.

A number of drug-related adverse events are common with drug-resistant TB treatment regimens. These events include gastrointestinal upset, rash, drug fever, and hepatitis. Although it is reasonable to continue therapy for mild reactions of gastrointestinal upset, rash, and hepatitis (asymptomatic elevation of serum aminotransferases < 5x upper limit of normal), stopping therapy should be used for more severe reactions. Because many of the standard drugs for treatment of tuberculosis can cause these reactions, all drugs for

treatment of tuberculosis including the investigational drug should be stopped simultaneously and restarted one at a time to explore which drug may be causing the reaction.¹⁰¹ The protocol should state the procedure for stopping and restarting antimycobacterial drugs and the order in which the drugs should be restarted.

Patients who require permanent discontinuation from the trial drug should continue to be followed per protocol for outcomes (i.e., patients should remain in the trial even if off the trial drug).

8.12. Size of Safety Database

The following is an excerpt from the Guidance for Industry “Premarketing Risk Assessment.”¹⁰²

GENERATING RISK INFORMATION DURING CLINICAL TRIALS

Providing detailed guidance on what constitutes an adequate safety database for all products is impossible. The nature and extent of safety data that would provide sufficient information about risk for purposes of approving a product are individualized decisions based on a number of factors (several of which are discussed below). In reaching a final decision on approvability, both existing risk information and any outstanding questions regarding safety are considered in a product’s risk assessment and weighed against the product’s demonstrated benefits. The fewer a product’s demonstrated benefits, the less acceptable may be higher levels of demonstrated risks. Likewise, the fewer the benefits, generally, the less uncertainty may be accepted about a product’s risks.

To maximize the information gained from clinical trials, FDA recommends that from the outset of development, sponsors pay careful attention to the overall design of the safety evaluation. Potential problems that may be suspected because of preclinical data or because of effects of related drugs should be targeted for evaluation. And, because it is impossible to predict every important risk, as experience accrues, sponsors should refine or modify their safety evaluations.

Size of the Premarketing Safety Database

Even large clinical development programs cannot reasonably be expected to identify all risks associated with a product. Therefore, it is expected that, even for a product that is rigorously tested preapproval, some risks will become apparent only after approval, when the product is used in tens of thousands or even millions of patients in the general population. Although no preapproval database can possibly be sized to detect all safety issues that might occur with the product once marketed in the full population, the larger and more comprehensive the preapproval database, the more likely it is that serious adverse events will be detected during drug development.

The appropriate size of a safety database supporting a new product will depend on a number of factors specific to that product, including:

¹⁰¹ This process is discussed in *Treatment of Tuberculosis* (Antimicrobial Susceptibility Test Systems, Centers for Disease Control, and Infectious Disease Society of America, 2003, MMWR 52: 1-77).

¹⁰² <http://www.fda.gov/cder/guidance/6357fnl.htm>

- Its novelty (i.e., whether it represents a new treatment or is similar to available treatment)
- The availability of alternative therapies and the relative safety of those alternatives as compared to the new product
- The intended population and condition being treated
- The intended duration of use

Safety databases for products intended to treat life-threatening diseases, especially in circumstances where there are no alternative satisfactory treatments, are usually smaller than for products intended to treat diseases that are neither life-threatening nor associated with major, irreversible morbidity. A larger safety database may be appropriate if a product's preclinical assessment or human clinical pharmacology studies identify signals of risk that warrant additional clinical data to properly define the risk. The appropriate size of the preapproval safety database may warrant specific discussion with the relevant review division. For instance, 21 CFR 312.82(b) (subpart E) provides that for drugs intended to treat life-threatening and seriously debilitating illnesses, end-of-phase 1 meetings can be used to agree on the design of phase 2 trials 'with the goal that such testing will be adequate to provide sufficient data on the drug's safety and effectiveness to support a decision on its approvability for marketing.'

For products intended for short-term or acute use (e.g., treatments that continue for, or are cumulatively administered for, less than 6 months), FDA believes it is difficult to offer general guidance on the appropriate target size of clinical safety databases. This is because of the wide range of indications and diseases (e.g., acute strokes to mild headaches) that may be targeted by such therapies. Sponsors are therefore encouraged to discuss with the relevant review division the appropriate size of the safety database for such products. Because products intended for life-threatening and severely debilitating diseases are often approved with relatively small safety databases, relatively greater uncertainty remains regarding their adverse effects. Similarly, when products offer a unique, clinically important benefit to a population or patient group, less certainty in characterizing risk prior to approval may be acceptable.

For products intended for long-term treatment of non-life-threatening conditions, (e.g., continuous treatment for 6 months or more or recurrent intermittent treatment where cumulative treatment equals or exceeds 6 months), the ICH and FDA have generally recommended that 1500 subjects be exposed to the investigational product (with 300 to 600 exposed for 6 months, and 100 exposed for 1 year).¹⁰³ For those products characterized as chronic use products in the ICH guidance E1A, FDA recommends that the 1500 subjects include only those who have been exposed to the product in multiple dose studies, because many adverse events of concern (e.g., hepatotoxicity, hematologic events) do not appear with single doses or very short-term exposure. Also, the 300 to 600 subjects exposed for 6 months and 100 subjects exposed for 1 year should have been exposed to relevant doses (i.e., doses generally in the therapeutic range).

We note that it is common for well-conducted clinical development programs to explore doses higher than those ultimately proposed for marketing. For example, a dose tested in clinical trials may offer no efficacy advantage and show some dose-related toxicities; therefore, the sponsor does not propose the dose for marketing when the application is submitted. In such cases, data from subjects exposed to doses in excess of those ultimately proposed are highly informative for the safety evaluation and should be counted as contributing to the relevant safety database...

8.13. Foreign Data

¹⁰³ Guidance for Industry E1A *The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions*, ICH.
www.fda.gov/cder/guidance/iche1a.pdf

Clinical trials of drug-resistant TB are likely to be conducted outside the US. Foreign studies performed under an investigational new drug application (IND) must meet the same requirements of 21 CFR Part 312 or 21 CFR Part 812, respectively, that apply to US studies conducted under an IND. Under 21 CFR 312.120(c)(1), FDA will accept a foreign clinical trials not conducted under an IND, if they were conducted in accordance with GCP and FDA is able to validate the data from the study through an onsite inspection, if necessary.¹⁰⁴

Food and Drug Administration (FDA) regulations also permit the acceptance of foreign clinical trials as the sole basis for marketing approval of a NDA if certain conditions are met: 1) The foreign data are applicable to the US population and US medical practice; (2) the studies have been performed by clinical investigators of recognized competence; and (3) the data may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA is able to validate the data through an on-site inspection or other appropriate means. Failure of an application to meet any of these criteria will result in the application not being approvable based on the foreign data alone.

9. Conclusions and Discussion for the Advisory Committee

The committee is being asked to discuss issues related to the development of drugs for the treatment of TB, specifically MDR-TB. Primary topics for discussion include specific issues related to study design, such as endpoints and duration of follow-up to assess outcome, and evaluation of drug safety.

Since MDR-TB is considered a serious and life-threatening disease the Accelerated Approval (Subpart H) regulations (21 CFR 314.500) may apply. As mentioned earlier in this document, approval may be granted on the basis of adequate and well-controlled clinical trials showing the drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or an effect on a clinical endpoint other than survival. As part of the accelerated approval regulations, sponsors are required to complete an assessment of long-term clinical benefit. Various early endpoints (e.g., sputum culture conversion, time to sputum conversion) for consideration along with their usefulness and limitations have been described in this document.

If particular early endpoint(s) related to MDR-TB disease can be identified as appropriate, it must also be decided the time point at which they should be assessed and whether or not the clinical benefit seen at the early time point adequately predicts long-term clinical outcome. Clinical outcome is generally measured by resolution of signs and symptoms, mortality and/or relapse of disease.

¹⁰⁴ Human Subject Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application Federal Register / Vol. 73, No. 82 / Monday, April 28, 2008 / Rules and Regulations, p 22801-13.

Consideration should also be given to studying HIV co-infected patients and whether the early endpoint(s) and timing of those endpoints, as discussed above, apply to the HIV-positive population, including the timing of an assessment of long-term clinical outcome.

In addition to efficacy considerations, the adequacy of the safety data used to support a drug application for MDR-TB, including the minimum size of a safety database for drugs approved under both accelerated and traditional approval mechanisms, should be assessed.

Please consider these questions in preparation for the meeting:

1. Which early endpoint(s) could provide evidence of efficacy on a clinically-meaningful outcome and thereby serve as the basis for a submission of a new drug to treat MDR-TB under Subpart H regulations (Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses [21 CFR 314.510])? At what time point should these endpoint(s) be assessed?
2. What clinical outcome should serve to confirm the early endpoint(s) for drugs approved under Subpart H regulations (e.g., mortality, relapse, or both)? In order to support traditional approval what is the appropriate timing of assessment of clinical outcome following the end of therapy? What level of evidence should be provided regarding relapse/mortality to support traditional approval (i.e., is a statistically meaningful difference needed or can the results simply be described)?
3. What should the minimum size of the safety database available before approval of a drug to treat MDR-TB? What factors would influence this recommendation (e.g., potential drug-drug interactions, other)? Should the size of the safety database be different for products approved based on an early endpoint (e.g., measured during therapy or at completion of therapy) vs. later endpoint (e.g., follow-up months off therapy)?
4. What factors would facilitate or limit inclusion of HIV-positive patients in trials for initial approval of drugs for MDRTB? Do the surrogate endpoint(s) and timing of accelerated approval, as discussed in #1 apply to the HIV-positive population? Should timing of the long-term clinical assessment be modified in trials of HIV-positive patients?

Appendices

- A. Table of HIV-negative subjects in MDR-TB Studies from the Literature**
- B. Table of HIV-positive subjects in MDR-TB Studies from the Literature**
- C. Bibliography of Studies Included in Tables**
- D. Concept Paper -- Pulmonary Tuberculosis: Developing Drugs for Treatment**